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(54) Title: NOVEL SURFACE PROTEIN OF <i>NEISSERIA MENINGITIDIS</i> (57) Abstract <p>The invention provides a novel surface polypeptide from <i>Neisseria meningitidis</i> as well as nucleic acid and nucleic acid sequence homologues encoding this protein. Pharmaceutical compositions containing the polypeptide and nucleic acids of the invention are also disclosed as well as methods useful in the treatment, prevention and diagnosis of <i>N. meningitidis</i> infection.</p>		

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TITLE

"NOVEL SURFACE ANTIGEN"

FIELD OF THE INVENTION

5 The present invention relates to novel polypeptides as for example obtainable from *Neisseria meningitidis*, to nucleotide sequences encoding such polypeptides, to the use of these in diagnostics, in therapeutic and prophylactic vaccines and in the
10 design and/or screening of medicaments.

BACKGROUND OF THE INVENTION

Neisseria meningitidis is a Gram-negative bacterium and the causative agent of meningococcal
15 meningitis and septicemia. Its only known host is the human, and it may be carried asymptotically by approximately 10% of the population (Caugant, D. et al, 1994, *Journal of Clinical Microbiology*, 32:323-30).

20 *N. meningitidis* may express a polysaccharide capsule, and this allows classification of the bacteria according to the nature of the capsule expressed. There are at least thirteen serogroups of *N. meningitidis*: A,B,C,29-E,H,I,K,L,W135,X,Y and Z, of
25 which serogroups A, B, and C cause 90% of meningococcal disease (Poolman, J.T. et al, 1995, *Infectious Agents and Disease*, 4:13-28). Vaccines directed against serogroups A and C are available, but the serogroup B capsular polysaccharide is poorly
30 immunogenic and does not induce protection in humans.

 Other membrane and extracellular components are therefore being examined for their suitability for

inclusion in vaccines. Examples include the outer membrane proteins of classes 1, 2 and 3 (porins), and classes 4 (Rmp) and 5 (Opacity proteins). However, to date, none of these candidates is able to induce complete protection, particularly in children (Romero, J.D., 1994, *Clinical Microbiology Review*, 7:559-575; Poolman, J.T. et al, 1995, *supra*).

To create an effective vaccine, it is necessary to identify components of *N. meningitidis* which are present in a majority of strains, and which are capable of inducing a protective immune response (bactericidal antibodies). In this regard, reference may be made to Brodeur et al. (International Publication WO 96/29412) who disclose a 22 kDa surface protein which is highly conserved across 99% of all known strains of *N. meningitidis*. Injection of purified recombinant 22 kDa surface protein protected 80% of immunized mice against development of a lethal infection by *N. meningitidis*. Notwithstanding the discovery of this protein, there is still a need to isolate more surface proteins of *N. meningitidis* which are highly conserved across a plurality of strains, and which have immuno-protective profiles against *N. meningitidis*, and/or which may be used in combination with other components of *N. meningitidis* to enhance the efficacy of protection against this organism.

SUMMARY OF THE INVENTION

The present inventors have discovered a new gene which is present in all tested strains of *N. meningitidis* and which encodes a novel polypeptide having a predicted molecular weight of about 62 kDa. Based upon its sequence characteristics and homologies, this polypeptide is predicted to be an

adhesin and this, together with experimental data suggests that it constitutes a surface protein which may be useful for the production of therapeutic and/or prophylactic vaccines against *N. meningitidis* as described hereinafter.

Accordingly, in one aspect of the invention, there is provided an isolated polypeptide or fragment thereof, or variant or derivative of these, said polypeptide selected from the group consisting of:

- (a) a polypeptide according to SEQ ID NO 2;
- (b) a polypeptide according to SEQ ID NO 5;
- (c) a polypeptide according to SEQ ID NO 7;
- (d) a polypeptide according to SEQ ID NO 9;
- (e) a polypeptide according to SEQ ID NO 11;
- (f) a polypeptide according to SEQ ID NO 13;
- (g) a polypeptide according to SEQ ID NO 15;
- (h) a polypeptide according to SEQ ID NO 17;
- (i) a polypeptide according to SEQ ID NO 19; and
- (j) a polypeptide according to SEQ ID NO 21.

Preferably, said polypeptide, fragment, variant or derivative displays immunological activity against one or more members selected from the group consisting of:-

- (i) *N. meningitidis*;
- (ii) said polypeptide;
- (iii) said fragment;
- (iv) said variant; and
- (v) said derivative;

According to another aspect, the invention provides an isolated nucleic acid sequence encoding a polypeptide or fragment thereof, or variant or derivative of said fragment or polypeptide, according to the first-mentioned aspect. Suitably, said sequence is selected from the group consisting of:

- (1) the nucleotide sequence of SEQ ID NO 1;
- (2) the nucleotide sequence of SEQ ID NO 3;
- (3) the nucleotide sequence of SEQ ID NO 4;
- 10 (4) the nucleotide sequence of SEQ ID NO 6;
- (5) the nucleotide sequence of SEQ ID NO 8;
- (6) the nucleotide sequence of SEQ ID NO 10;
- (7) the nucleotide sequence of SEQ ID NO 12;
- (8) the nucleotide sequence of SEQ ID NO 14;
- 15 (9) the nucleotide sequence of SEQ ID NO 16;
- (10) the nucleotide sequence of SEQ ID NO 18;
- (11) the nucleotide sequence of SEQ ID NO 20;
- (12) a nucleotide sequence fragment of any one of SEQ ID NOS 1, 3, 4, 6, 8, 10, 12, 14, 16, 18 and 20; and
- 20 (13) a nucleotide sequence homologue of any of the foregoing sequences

Preferably, said sequences encode a product displaying immunological activity against one or more members selected from the group consisting of:-

- (i) *N. meningitidis*;
- (ii) said polypeptide of the first-mentioned aspect;
- (iii) said fragment of said first-mentioned aspect;
- 30 (iv) said variant of said first-mentioned aspect; and
- (v) said derivative of said first-mentioned aspect.

In yet another aspect, the invention resides in an expression vector comprising a nucleic acid sequence according to the second-mentioned aspect wherein said sequence is operably linked to transcriptional and translational regulatory nucleic acid.

In a further aspect, the invention provides a host cell containing an expression vector according to the third-mentioned aspect.

In yet a further aspect of the invention, there is provided a method of producing a recombinant polypeptide according to the first-mentioned aspect, said method comprising the steps of:

(A) culturing a host cell containing an expression vector according to the third-mentioned aspect such that said recombinant polypeptide is expressed from said nucleic acid; and

(B) isolating said recombinant polypeptide.

In a still further aspect, the invention provides an antibody or fragment thereof that binds to one or more members selected from the group consisting of:-

- (1) *N. meningitidis*;
- (2) said polypeptide of the first-mentioned aspect;
- (3) said fragment of the first-mentioned aspect;
- (4) said variant of the first-mentioned aspect; and
- (5) said derivative of the first-mentioned aspect.

In yet another aspect, the invention provides a method of detecting *N. meningitidis* in a biological

sample suspected of containing same, said method comprising the steps of:-

- (A) isolating the biological sample from a patient;
- 5 (B) mixing the above-mentioned antibody or fragment with the biological sample to form a mixture; and
- (C) detecting specifically bound antibody or bound fragment in the mixture which
10 indicates the presence of *N. meningitidis*.

According to a further aspect, there is provided a method of detecting *N. meningitidis* bacteria in a biological sample suspected of
15 containing said bacteria, said method comprising the steps of:-

- (I) isolating the biological sample from a patient;
- (II) detecting a nucleic acid sequence
20 according to the second-mentioned aspect in said sample which indicates the presence of said bacteria.

The invention further contemplates a method for diagnosing infection of patients by *N. meningitidis*, said method comprising the steps of:-
25

- (1) contacting a biological sample from a patient with a polypeptide, fragment, variant or derivative of the invention; and
- 30 (2) determining the presence or absence of a complex between said polypeptide, fragment, variant or derivative and *N. meningitidis*-specific antibodies in said sample, wherein the presence of

said complex is indicative of said infection.

The invention also extends to the use of the polypeptide according to the first-mentioned aspect, the use of the nucleic acids according to the second-mentioned aspect or the use of the antibody or antibody fragment mentioned above in a kit for detecting *N. meningitidis* bacteria in a biological sample.

According to a further aspect of the invention, there is provided a pharmaceutical composition comprising an isolated polypeptide or fragment thereof, or a variant or derivative of these, according to the first mentioned aspect.

Preferably, said pharmaceutical composition is a vaccine.

In yet a further aspect, the invention provides a method of preventing infection of a patient by *N. meningitidis*, comprising the step of administering a pharmaceutically effective amount of the above-mentioned vaccine.

In a further aspect, the invention provides a method of identifying an immunoreactive fragment of a polypeptide, variant or derivatives according to the first mentioned aspect, comprising the steps of:-

- (a) generating a fragment of said polypeptide, variant or derivative;
- (b) administering said fragment to a mammal; and
- (c) detecting an immune response in said mammal which response includes production of elements which specifically bind *N. meningitidis* and/or said polypeptide, variant or

derivative, and/or a protective effect against *N. meningitidis* infection.

BRIEF DESCRIPTION OF THE DRAWINGS

5 "FIG. 1 depicts plasmid maps and cloning strategy. Primers A3A and A3B (SEQ ID NOS 28 and 29, respectively) were used to amplify from MC58 the region identified in the TIGR database as a homologue of AIDA-I". PCR product was cloned to give pNMAIDA3.
10 Primers A3C (SEQ ID NO 30) and A3D (SEQ ID NO 31) were used in inverse PCR to amplify a 3kbp *EagI* fragment encompassing *hiaNm*. This product was cloned to give piEAGA3. piEAGA3 was subcloned to give piEagA3.8 and piEagA3.9. Primers HiaNm:M and HiaNm:P (SEQ ID NOS 22
15 and 23, respectively) were used to amplify the contiguous region from MC58 and the product cloned to create pHiaNm. Primers Hia-MBPA (SEQ ID NO 24) and Hia-MBPB (SEQ ID NO 25) were used to amplify the open reading frame of *hiaNm*, and the product was cloned
20 into pMALC2 to create pMBP-HiaNm;

FIG. 2 is a Southern blot of genomic DNA of a number of strains of *N. meningitidis*. 2A: serogroup B strains. Lane 1 PMC28, Lane 2 PMC27, Lane 3 PMC25, Lane 4 PMC24, Lane 5 PMC16, Lane 6 PMC13, Lane 7
25 PMC12, Lane 8 MWt standards, Lane 9 2970, Lane 10 1000, Lane 11 528 Lane 12 SWZ107, Lane 13 H41, Lane 14 H38, Lane 15 NGH36, Lane 16 H15, Lane 17 NGG40, Lane 18 NGF26, Lane 19 NGE30, Lane 20 Lane NGE28 2B: Strains of serogroups other than B. Lane 1 PMC3, Lane
30 2 PMC17, Lane 3 PMC20, Lane 4 PMC23, Lane 5 PMC8, Lane 6 PMC9, Lane 7 PMC11, Lane 8 PMC14, Lane 9 PMC18, Lane 10 PMC21, Lane 11 PMC29, Lane 12 MWt standards, Lane 13 PMC19, Lane 14 PMC1, Lane 15 PMC6, Lane 16 PMC10, Lane 17 PMC22, Lane 18 PMC26, Lane 19 PMC2. Molecular

weight markers indicated in kilobase pairs (kb). Genomic DNA was hybridized with a probe corresponding to ntp 276-2054 of SEQ ID NO 1;

FIG. 3 shows a Coomassie stained gel of MBP-HiaNm. Cells containing pMALC2 (Lane 2) or pMBP-HiaNm (Lane 3) after induction with IPTG. Lane 1 molecular weight standards (kDa). Arrows indicate MBP and MBP-HiaNm;

FIG. 4 is a western blot of MC58 and MC58ΔHiaNm proteins incubated with rabbit immune sera. Lane 1; molecular weight standards indicated in kDa, Lane 2 total cellular protein of MC58, Lane 3 total cellular protein of MC58ΔHiaNm Lane 4, OMC preparation of MC58, Lane 5 OMC preparation of MC58ΔHiaNm, each lane contained 50 μL of protein suspension of A₂₈₀= 3.75;

FIG. 5 shows a Coomassie stained gel run in parallel to the gel that was Western blotted in FIG 4. Lanes are the same as for FIG 4;

FIG. 6 shows a sequence comparison of polypeptides of HiaNm, Hia, Hsf using the PILEUP alignment program; and

FIG. 7 shows a sequence comparison of polypeptide sequences of HiaNm from 10 strains of *N. meningitidis* using the PILEUP program

DETAILED DESCRIPTION OF THE INVENTION

Throughout this specification and the appendant claims, unless the context requires otherwise, the words "comprise", "comprises" and "comprising" will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

Polypeptide sequences

The present invention provides an isolated polypeptide according to SEQ ID NOS 2, 5, 7, 9, 11, 13, 15, 17, 19 and 21, or fragment respectively thereof, or variant or derivative of these. In a preferred embodiment, the polypeptide, fragments, variants and derivatives of the invention display immunological activity against any one member selected from the group consisting of *N. meningitidis*, said polypeptide, said fragment, said variant and said derivative.

SEQ ID NO 2 corresponds to the novel about 62 kDa surface polypeptide of the *hiaNm* gene obtained from *N. meningitidis* strain MC58, as described more fully hereinafter. SEQ ID NOS 5, 7, 9, 11, 13, 15, 17, 19, and 21 correspond to homologous polypeptides deduced from nucleotide sequences obtained from *N. meningitidis* strains BZ10, BZ198, EG327, EG329, H15, H38, H41, P20, and PMC21, respectively.

For the purposes of this invention, the term "immunological activity" refers to the ability of the aforementioned polypeptide, fragment, variant or derivative to produce an immune response in a mammal to which it is administered, wherein the response includes the production of elements which specifically bind *N. meningitidis* and/or said polypeptide, fragment, variant or derivative, and/or a protective effect against *N. meningitidis* infection.

By "isolated" is meant material which is substantially or essentially free from components which normally accompany it in its native state.

By "polypeptide" is meant long chain peptides including proteins.

As used herein, the term "fragment" includes deletion mutants and small peptides, for example of at least 6, preferably at least 10 and more preferably at least 20 amino acids in length, which comprise antigenic determinants or epitopes. Several such fragments may be joined together. Peptides of this type may be obtained through the application of standard recombinant nucleic acid techniques or synthesized using conventional liquid or solid phase synthesis techniques. For example, reference may be made to solution synthesis or solid phase synthesis as described, for example, in Chapter 9 entitled "Peptide Synthesis" by Atherton and Shephard which is included in a publication entitled "Synthetic Vaccines" edited by Nicholson and published by Blackwell Scientific Publications. Alternatively, peptides can be produced by digestion of a polypeptide of the invention with proteinases such as endoLys-C, endoArg-C, endoGlu-C and staphylococcins V8-protease. The digested fragments can be purified by, for example, high performance liquid chromatographic (HPLC) techniques.

The term "variant" refers to polypeptides in which one or more amino acids have been replaced by different amino acids. It is well understood in the art that some amino acids may be changed to others with broadly similar properties without changing the nature of the activity of the polypeptide (conservative substitutions). Exemplary conservative substitutions in the polypeptide may be made according to the following table:

TABLE 1

Original Residue	Exemplary Substitutions
Ala	Ser

Arg	Lys
Asn	Gln, His
Asp	Glu
Cys	Ser
Gln	Asn
Glu	Asp
Gly	Pro
His	Asn, Gln
Ile	Leu, Val
Leu	Ile, Val
Lys	Arg, Gln, Glu
Met	Leu, Ile,
Phe	Met, Leu, Tyr
Ser	Thr
Thr	Ser
Trp	Tyr
Tyr	Trp, Phe
Val	Ile, Leu

Substantial changes in function are made by selecting substitutions that are less conservative than those shown in TABLE 1. Other replacements would be non-conservative substitutions and relatively fewer of these may be tolerated. Generally, the substitutions which are likely to produce the greatest changes in a polypeptide's properties are those in which (a) a hydrophilic residue (e.g., Ser or Thr) is substituted for, or by, a hydrophobic residue (e.g., Ala, Leu, Ile, Phe or Val); (b) a cysteine or proline is substituted for, or by, any other residue; (c) a residue having an electropositive side chain (e.g., Arg, His or Lys) is substituted for, or by, an electronegative residue (e.g., Glu or Asp) or (d) a residue having a bulky side chain (e.g., Phe or Trp) is substituted for, or by, one having a smaller side chain (e.g., Ala, Ser) or no side chain (e.g., Gly).

In general, variants will be at least 75% homologous, more suitably at least 80%, preferably at least 85%, and most preferably at least 90% homologous to the basic sequences as for example shown in SEQ ID NOS 2, 5, 7, 9, 11, 13, 15, 17, 19 and 21. Homology is defined as the percentage number of amino acids which are identical or constitute conservative substitutions as defined in Table 1. Homology may be determined using sequence comparison programs such as GAP (Deveraux et al. 1984, *Nucleic Acids Research* 12, 387-395) which is incorporated herein by reference. In this way sequences of a similar or substantially different length to those cited herein may be compared by insertion of gaps into the alignment, such gaps being determined, for example, by the comparison algorithm used by GAP. What constitutes suitable variants may be determined by conventional techniques. For example, nucleic acids encoding polypeptides according to SEQ ID NOS 2, 5, 7, 9, 11, 13, 15, 17, 19 and 21 can be mutated using either random mutagenesis for example using transposon mutagenesis, or site-directed mutagenesis. The resultant DNA fragments are then cloned into suitable expression hosts such as *E. coli* using conventional technology and clones which retain the desired activity are detected. Where the clones have been derived using random mutagenesis techniques, positive clones would have to be sequenced in order to detect the mutation. The term "variant" also includes naturally occurring allelic variants.

By "derivative" is meant a polypeptide which has been derived from the basic sequence by modification, for example by conjugation or complexing with other chemical moieties or by post-translational modification techniques as would be understood in the

art. Such derivatives include amino acid deletions and/or additions to polypeptides according to SEQ ID NOS 2, 5, 7, 9, 11, 13, 15, 17, 19 and 21 or variants thereof wherein said derivatives retain immunological activity. "Additions" of amino acids may include fusion of the polypeptides or variants thereof with other polypeptides or proteins. In this regard, it will be appreciated that the polypeptides or variants of the invention may be incorporated into larger polypeptides, and such larger polypeptides may also be expected to retain immunological activity against, for example, *N. meningitidis*. The polypeptides as described above may be fused to a further protein, for example, which is not derived from *N. meningitidis*. The other protein may, by way of example, assist in the purification of the protein. For instance a polyhistidine tag, or a maltose binding protein may be used in this respect as described in more detail below. Alternatively, it may produce an immune response which is effective against *N. meningitidis* or it may produce an immune response against another pathogen. Other possible fusion proteins are those which produce an immunomodulatory response. Particular examples of such proteins include Protein A or glutathione S-transferase (GST). In addition, the polypeptide may be fused to an oligosaccharide based vaccine component where it acts as a carrier protein.

Other derivatives contemplated by the invention include, but are not limited to, modification to side chains, incorporation of unnatural amino acids and/or their derivatives during peptide, polypeptide or protein synthesis and the use of crosslinkers and other methods which impose conformational constraints on the polypeptides, fragments and variants of the invention.

Examples of side chain modifications contemplated by the present invention include modifications of amino groups such as by acylation with acetic anhydride; acylation of amino groups with succinic anhydride and tetrahydrophthalic anhydride; amidination with methylacetimidate; carbamoylation of amino groups with cyanate; pyridoxylation of lysine with pyridoxal-5-phosphate followed by reduction with NaBH_4 ; reductive alkylation by reaction with an aldehyde followed by reduction with NaBH_4 ; and trinitrobenzylation of amino groups with 2, 4, 6-trinitrobenzene sulphonic acid (TNBS).

The carboxyl group may be modified by carbodiimide activation via O-acylisourea formation followed by subsequent derivitization, by way of example, to a corresponding amide.

The guanidine group of arginine residues may be modified by formation of heterocyclic condensation products with reagents such as 2,3-butanedione, phenylglyoxal and glyoxal.

Sulphydryl groups may be modified by methods such as performic acid oxidation to cysteic acid; formation of mercurial derivatives using 4-chloromercuriphenylsulphonic acid, 4-chloromercuribenzoate; 2-chloromercuri-4-nitrophenol, phenylmercury chloride, and other mercurials; formation of a mixed disulphides with other thiol compounds; reaction with maleimide, maleic anhydride or other substituted maleimide; carboxymethylation with iodoacetic acid or iodoacetamide; and carbamoylation with cyanate at alkaline pH.

Tryptophan residues may be modified, for example, by alkylation of the indole ring with 2-hydroxy-5-nitrobenzyl bromide or sulphonyl halides or by oxidation with N-bromosuccinimide.

Tyrosine residues, may be modified by nitration with tetranitromethane to form a 3-nitrotyrosine derivative.

5 The imidazole ring of a histidine residue may be modified by N-carbethoxylation with diethylpyrocarbonate or by alkylation with iodoacetic acid derivatives.

Examples of incorporating unnatural amino acids and derivatives during peptide synthesis include
 10 but are not limited to, use of 4-amino butyric acid, 6-aminohexanoic acid, 4-amino-3-hydroxy-5-phenylpentanoic acid, 4-amino-3-hydroxy-6-methylheptanoic acid, t-butylglycine, norleucine, norvaline, phenylglycine, ornithine, sarcosine, 2-
 15 thienyl alanine and/or D-isomers of amino acids. A list of unnatural amino acids contemplated by the present invention is shown in TABLE 2.

TABLE 2

Non-conventional amino acid	Non-conventional amino acid
α -aminobutyric acid	L-N-methylalanine
α -amino- α -methylbutyrate	L-N-methylarginine
aminocyclopropane-carboxylate	L-N-methylasparagine
aminoisobutyric acid	L-N-methylaspartic acid
aminonorbornyl-carboxylate	L-N-methylcysteine
cyclohexylalanine	L-N-methylglutamine
cyclopentylalanine	L-N-methylglutamic acid
L-N-methylisoleucine	L-N-methylhistidine
D-alanine	L-N-methylleucine
D-arginine	L-N-methyllysine
D-aspartic acid	L-N-methylmethionine
D-cysteine	L-N-methylnorleucine
D-glutamate	L-N-methylnorvaline
D-glutamic acid	L-N-methylornithine
D-histidine	L-N-methylphenylalanine
D-isoleucine	L-N-methylproline
D-leucine	L-N-methylserine

D-lysine	L-N-methylthreonine
D-methionine	L-N-methyltryptophan
D-ornithine	L-N-methyltyrosine
D-phenylalanine	L-N-methylvaline
D-proline	L-N-methylethylglycine
D-serine	L-N-methyl-t-butylglycine
D-threonine	L-norleucine
D-tryptophan	L-norvaline
D-tyrosine	α -methyl-aminoisobutyrate
D-valine	α -methyl- γ -aminobutyrate
D- α -methylalanine	α -methylcyclohexylalanine
D- α -methylarginine	α -methylcyclopentylalanine
D- α -methylasparagine	α -methyl- α -naphthylalanine
D- α -methylaspartate	α -methylpenicillamine
D- α -methylcysteine	N-(4-aminobutyl)glycine
D- α -methylglutamine	N-(2-aminoethyl)glycine
D- α -methylhistidine	N-(3-aminopropyl)glycine
D- α -methylisoleucine	N-amino- α -methylbutyrate
D- α -methyllleucine	α -naphthylalanine
D- α -methyllysine	N-benzylglycine
D- α -methylmethionine	N-(2-carbamylethyl)glycine
D- α -methylornithine	N-(carbamylmethyl)glycine
D- α -methylphenylalanine	N-(2-carboxyethyl)glycine
D- α -methylproline	N-(carboxymethyl)glycine
D- α -methylserine	N-cyclobutylglycine
D- α -methylthreonine	N-cycloheptylglycine
D- α -methyltryptophan	N-cyclohexylglycine
D- α -methyltyrosine	N-cyclodecylglycine
L- α -methyllleucine	L- α -methyllysine
L- α -methylmethionine	L- α -methylnorleucine
L- α -methylnorvaline	L- α -methylornithine
L- α -methylphenylalanine	L- α -methylproline
L- α -methylserine	L- α -methylthreonine
L- α -methyltryptophan	L- α -methyltyrosine
L- α -methylvaline	L-N-methylhomophenylalanine
N-(N-(2,2-diphenylethyl	N-(N-(3,3-diphenylpropyl

carbamylmethyl)glycine 1-carboxy-1-(2,2-diphenyl-ethyl amino) cyclopropane	carbamylmethyl)glycine
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The invention also contemplates covalently modifying a polypeptide, fragment or variant of the invention with dinitrophenol, in order to render it immunogenic in humans

Preferably the invention comprises a polypeptide selected from any one of the polypeptides according to SEQ ID NOS 2, 5, 7, 9, 11, 13, 15, 17, 19 and 21.

Polypeptides of the inventions may be prepared by any suitable procedure known to those of skill in the art. For example, the polypeptides may be prepared by a procedure including the steps of:

(a) preparing a recombinant nucleic acid containing a nucleotide sequence encoding a polypeptide according to any one of SEQ ID NOS 2, 5, 7, 9, 11, 13, 15, 17, 19 and 21, or fragment thereof, or variant or derivative of these, which nucleotide sequence is operably linked to transcriptional and translational regulatory nucleic acid;

(b) transfecting or transforming a suitable host cell with the recombinant nucleic acid;

(c) culturing the host cell to express recombinant polypeptide from said recombinant nucleic acid; and

(d) isolating the recombinant polypeptide.

Suitably said nucleotide sequence is selected from the group consisting of SEQ ID NOS 1, 3, 4, 6, 8, 10, 12, 14, 16, 18 and 20.

By "recombinant polypeptide" is meant a polypeptide made using recombinant techniques, i.e., through the expression of a recombinant nucleic acid.

The term "*recombinant nucleic acid*" as used herein refers to nucleic acid formed *in vitro* by the manipulation of nucleic acid into a form not normally found in nature. In this regard, the recombinant nucleic acid preferably comprises an expression vector which may be either a self-replicating extra-chromosomal vector such as a plasmid, or a vector which integrates into a host genome. Generally, such expression vectors include transcriptional and translational regulatory nucleic acid operably linked to the said nucleotide sequence.

By "*operably linked*" is meant that the transcriptional and translational regulatory nucleic acid is positioned relative to the nucleotide sequence encoding the said polypeptide, fragment, variant or derivative in such a manner that such transcription is initiatable. The transcriptional and translational regulatory nucleic acid will generally be appropriate for the host cell used for expression. Numerous types of appropriate expression vectors, and suitable regulatory sequences are known in the art for a variety of host cells.

Typically, the transcriptional and translational regulatory nucleic acid may include, but is not limited to, promoter sequences, leader or signal sequences, ribosomal binding sites, transcriptional start and stop sequences, translational start and stop sequences, and enhancer or activator sequences.

Constitutive or inducible promoters as known in the art are contemplated by the invention. The promoters may be either naturally occurring promoters, or hybrid promoters which combine elements of more than one promoter.

In a preferred embodiment, the expression vector contains a selectable marker gene to allow the selection of transformed host cells. Selection genes are well known in the art and will vary with the host cell used.

The expression vector may also include a fusion partner (typically provided by the expression vector) so that the recombinant polypeptide of the invention is expressed as a fusion polypeptide with said fusion partner. The main advantage of fusion partners is that they assist identification and/or purification of said fusion polypeptide.

In order to express said fusion polypeptide, it is necessary to ligate a nucleotide sequence according to the invention into the expression vector so that the translational reading frames of the fusion partner and the nucleotide sequence of the invention coincide.

Well known examples of fusion partners include, but are not limited to, glutathione-S-transferase (GST), Fc portion of human IgG, maltose binding protein (MBP) and hexahistidine (HIS₆), which are particularly useful for isolation of the fusion polypeptide by affinity chromatography. For the purposes of fusion polypeptide purification by affinity chromatography, relevant matrices for affinity chromatography are glutathione-, amylose-, and nickel- or cobalt-conjugated resins respectively. Many such matrices are available in "kit" form, such as the QIAexpress™ system (Qiagen) useful with (HIS₆) fusion partners and the Pharmacia GST purification system.

Another fusion partner well known in the art is green fluorescent protein (GFP). This fusion partner serves as a fluorescent "tag" which allows the

fusion polypeptide of the invention to be identified by fluorescence microscopy or by flow cytometry. The GFP tag is useful when assessing subcellular localization of the fusion polypeptide of the invention, or for isolating cells which express the fusion polypeptide of the invention. Flow cytometric methods such as fluorescence activated cell sorting (FACS) are particularly useful in this latter application.

Preferably, the fusion partners also have protease cleavage sites, such as for Factor X_a or Thrombin, which allow the relevant protease to partially digest the fusion polypeptide of the invention and thereby liberate the recombinant polypeptide of the invention therefrom. The liberated polypeptide can then be isolated from the fusion partner by subsequent chromatographic separation.

Fusion partners according to the invention also include within their scope "epitope tags", which are usually short peptide sequences for which a specific antibody is available. Well known examples of epitope tags for which specific monoclonal antibodies are readily available include c-myc, influenza virus haemagglutinin and FLAG tags.

Recombinant polypeptides of the invention may be produced by culturing a host cell transformed with an expression vector containing nucleic acid encoding a polypeptide, fragment, variant or derivative according to the invention. The conditions appropriate for protein expression will vary with the choice of expression vector and the host cell. This is easily ascertained by one skilled in the art through routine experimentation.

Suitable host cells for expression may be prokaryotic or eukaryotic. One preferred host cell

for expression of a polypeptide according to the invention is a bacterium. The bacterium used may be *Escherichia coli*. Alternatively, the host cell may be an insect cell such as, for example, SF9 cells which may be utilized with a baculovirus expression system.

The recombinant protein may be conveniently prepared by a person skilled in the art using standard protocols as for example described in Sambrook, et al., MOLECULAR CLONING. A LABORATORY MANUAL (Cold Spring Harbor Press, 1989), incorporated herein by reference, in particular Sections 16 and 17; Ausubel et al., CURRENT PROTOCOLS IN MOLECULAR BIOLOGY (John Wiley & Sons, Inc. 1994-1998), incorporated herein by reference, in particular Chapters 10 and 16; and Coligan et al., CURRENT PROTOCOLS IN PROTEIN SCIENCE (John Wiley & Sons, Inc. 1995-1997) which is incorporated by reference herein, in particular Chapters 1, 5 and 6.

Nucleotide sequences

The invention further provides a nucleotide sequence which encodes a polypeptide, fragment, variant or derivative as defined above. Suitably said sequence is selected from the group consisting of:- SEQ ID NOS 1, 3, 4, 6, 8, 10, 12, 14, 16, 18 and 20; a nucleotide sequence fragment of any one of SEQ ID NOS 1, 3, 4, 6, 8, 10, 12, 14, 16, 18 and 20; and a nucleotide sequence homologue of the foregoing sequences. Preferably, these sequences encode a product displaying immunological activity as defined above.

As will be more fully described hereinafter, SEQ ID NO 1 corresponds to the *hlaNm* gene obtained from *N. meningitidis* strain MC58. This gene encodes

the novel 62 kDa (approximately) surface polypeptide of SEQ ID NO 2. SEQ ID NO 3 corresponds to the *hlaNm* open reading frame sequence of strain MC58, *HlaNm*. SEQ ID NOS 4, 6, 8, 10, 12, 14, 16, 18, and 20 correspond to the homologous *hlaNm* open reading frame sequences obtained from *N. meningitidis* strains BZ10, BZ198, EG327, EG329, H15, H38, H41, P20, and PMC21, respectively.

The term "nucleotide sequence" as used herein designates mRNA, RNA, cRNA, cDNA or DNA.

The term "nucleotide sequence homologues" generally refers to nucleotide sequences which hybridize with a wild-type nucleotide sequence according to the invention under substantially stringent conditions. Suitable hybridization conditions will be discussed hereinafter.

The nucleotide sequence homologues of the invention may be prepared according to the following procedure:

- (i) obtaining a nucleic acid extract from a suitable host;
- (ii) creating primers which are optionally degenerate wherein each comprises a portion of a wild-type nucleotide sequence of the invention; and
- (iii) using said primers to amplify, via nucleic acid amplification techniques, one or more amplification products from said nucleic acid extract.

Suitably, the host may be a bacterium. Preferably, the host is from the genus *Neisseria*, more preferably from *N. meningitidis*.

Preferably, the primers are selected from the group consisting of:-

- (1) 5'-TTAGATTCCACGTCCCAGATT-3' (SEQ ID NO 22);
- 5 (2) 5'-CTTCCCTTCAAACCTTCC-3' (SEQ ID NO 23);
- (3) 5'-GGTCGCGGATCCATGAACAAAATATACCGCAT-3' (SEQ ID NO 24);
- (4) 5'-TCACCCAAGCTTAAGCCCTTACCACTGATAAC-3' (SEQ ID NO 25);
- 10 (5) 5'-CCAAACCCCGATTTAACC-3' (SEQ ID NO 26);
- (6) 5'-AATCGCCACCCTTCCCTTC-3' (SEQ ID NO 27);
- 15 (7) 5'-TTTGCAACGGTTCAGGCA-3' (SEQ ID NO 28);
- (8) 5'-TATTCAGCAGCGTATCGG-3' (SEQ ID NO 29);
- (9) 5'-TGCCTGAACCGTTGCAAA-3' (SEQ ID NO 30); and
- 20 (10) 5'-CCGATACGCTGCTGAATA-3' (SEQ ID NO 31).

Suitable nucleic acid amplification techniques are well known to the skilled addressee, and include polymerase chain reaction (PCR) as for example described in Ausubel et al. (1994-1998, *supra*, Chapter 15) which is incorporated herein by reference; strand displacement amplification (SDA) as for example described in U.S. Patent No 5,422,252 which is incorporated herein by reference; rolling circle replication (RCR) as for example described in Liu et al., (1996, *J. Am. Chem. Soc.* 118:1587-1594 and International application WO 92/01813) and Lizardi et al., (International Application WO 97/19193) which are

incorporated herein by reference; nucleic acid sequence-based amplification (NASBA) as for example described by Sooknanan et al., (1994, *Biotechniques* 17:1077-1080) which is incorporated herein by reference; and Q- β replicase amplification as for example described by Tyagi et al., (1996, *Proc. Natl. Acad. Sci. USA* 93:5395-5400) which is incorporated herein by reference.

As used herein, an "amplification product" refers to a nucleic acid product generated by nucleic acid amplification techniques.

"Hybridize" or "hybridization" is used here to denote the pairing of complementary bases of distinct nucleotide sequences to produce a DNA-DNA hybrid, a DNA-RNA hybrid, or an RNA-RNA hybrid according to base-pairing rules.

In DNA, complementary bases are:

- (i) A and T; and
- (ii) C and G.

In RNA, complementary bases are:

- (i) A and U; and
- (ii) C and G.

In RNA-DNA hybrids, complementary bases are:

- (i) A and U;
- (ii) A and T; and
- (iii) G and C.

Typically, substantially complementary nucleotide sequences are identified by blotting techniques that include a step whereby nucleotides are immobilized on a matrix (preferably a synthetic membrane such as nitrocellulose), a hybridization step, and a detection step. Southern blotting is used to identify a complementary DNA sequence; northern blotting is used to identify a complementary RNA

sequence. Dot blotting and slot blotting can be used to identify complementary DNA/DNA, DNA/RNA or RNA/RNA polynucleotide sequences. Such techniques are well known by those skilled in the art, and have been described in Ausubel et al. (1994-1998, *supra*) at pages 2.9.1 through 2.9.20.

According to such methods, Southern blotting involves separating DNA molecules according to size by gel electrophoresis, transferring the size-separated DNA to a synthetic membrane, and hybridizing the membrane bound DNA to a complementary nucleotide sequence labeled radioactively, enzymatically or fluorochromatically. In dot blotting and slot blotting, DNA samples are directly applied to a synthetic membrane prior to hybridization as above.

An alternative blotting step is used when identifying complementary nucleotide sequences in a cDNA or genomic DNA library, such as through the process of plaque or colony hybridization. A typical example of this procedure is described in Sambrook et al., (1989, *supra*) Chapters 8-12.

Typically, the following general procedure can be used to determine hybridization conditions. Nucleotide sequences are blotted/transferred to a synthetic membrane, as described above. A wild type nucleotide sequence of the invention is labeled as described above, and the ability of this labeled nucleotide sequence to hybridize with an immobilized nucleotide sequence analyzed.

A skilled addressee will recognize that a number of factors influence hybridization. The specific activity of radioactively labeled polynucleotide sequence should typically be greater than or equal to about 10^8 dpm/mg to provide a detectable signal. A radiolabeled nucleotide sequence

of specific activity 10^8 to 10^9 dpm/mg can detect approximately 0.5 pg of DNA. It is well known in the art that sufficient DNA must be immobilized on the membrane to permit detection. It is desirable to have excess immobilized DNA, usually 10 μ g. Adding an inert polymer such as 10% (w/v) dextran sulfate (MW 500,000) or polyethylene glycol 6000 during hybridization can also increase the sensitivity of hybridization (see Ausubel *supra* at 2.10.10).

To achieve meaningful results from hybridization between a nucleotide sequence immobilized on a membrane and a labeled nucleotide sequence, a sufficient amount of the labeled nucleotide sequence must be hybridized to the immobilized nucleotide sequence following washing. Washing ensures that the labeled nucleotide sequence is hybridized only to the immobilized nucleotide sequences with a desired degree of complementarity to the labeled nucleotide sequence.

"Stringency" as used herein, refers to the temperature and ionic strength conditions, and presence or absence of certain organic solvents, during hybridization. The higher the stringency, the higher will be the degree of complementarity between the immobilized nucleotide sequences and the labeled polynucleotide sequence.

"Stringent conditions" designates those conditions under which only nucleotide sequences having a high frequency of complementary bases will hybridize.

Typical stringent conditions include, for example, (1) 0.75 M dibasic sodium phosphate/0.5 M monobasic sodium phosphate/1 mM disodium EDTA/1% sarkosyl at about 42°C for at least 30 minutes; or (2)

6.0 M urea/0.4 % sodium lauryl sulfate/0.1x SSC at about 42°C for at least 30 minutes; or (3) 0.1x SSC/0.1% SDS at about 68°C for at least 20 minutes; or (4) 1x SSC/0.1% SDS at about 55°C for about 60 minutes; or (5) 1x SSC/0.1% SDS at about 62°C for about 60 minutes; or (6) 1x SSC/0.1% SDS at about 68°C for about 60 minutes; or (7) 0.2X SSC/0.1% SDS at about 55°C for about 60 minutes; or (8) 0.2x SSC/0.1% SDS at about 62°C for about one hour; or (9) 0.2X SSC/0.1% SDS at about 68°C for about 60 minutes. For a detailed example, see CURRENT PROTOCOLS IN MOLECULAR BIOLOGY *supra* at pages 2.10.1 to 2.10.16, and Sambrook et al. in MOLECULAR CLONING. A LABORATORY MANUAL (Cold Spring Harbour Press, 1989) at sections 1.101 to 1.104, which are hereby incorporated by reference.

While stringent washes are typically carried out at temperatures from about 42°C to 68°C, one skilled in the art will appreciate that other temperatures may be suitable for stringent conditions. Maximum hybridization typically occurs at about 20°C to 25°C below the T_m for formation of a DNA-DNA hybrid. It is well known in the art that the T_m is the melting temperature, or temperature at which two complementary polynucleotide sequences dissociate. Methods for estimating T_m are well known in the art (see CURRENT PROTOCOLS IN MOLECULAR BIOLOGY *supra* at page 2.10.8). Maximum hybridization typically occurs at about 10°C to 15°C below the T_m for a DNA-RNA hybrid.

Other stringent conditions are well-known in the art. A skilled addressee will recognize that various factors can be manipulated to optimize the specificity of the hybridization. Optimization of the stringency of the final washes can serve to ensure a high degree of hybridization.

Methods for detecting labeled nucleotide sequences hybridized to an immobilized nucleotide sequence are well known to practitioners in the art. Such methods include autoradiography, chemiluminescent, fluorescent and colorimetric detection.

Antibodies

The invention also contemplates antibodies against the aforementioned polypeptides, fragments, variants and derivatives. Such antibodies may include any suitable antibodies which bind to or conjugate with a polypeptide, fragment, variant or derivative of the invention. For example, the antibodies may comprise polyclonal antibodies. Such antibodies may be prepared for example by injecting a polypeptide, fragment, variant or derivative of the invention into a production species, which may include mice or rabbits, to obtain polyclonal antisera. Methods of producing polyclonal antibodies are well known to those skilled in the art. Exemplary protocols which may be used are described for example in Coligan et al., CURRENT PROTOCOLS IN IMMUNOLOGY, (John Wiley & Sons, Inc, 1991) which is incorporated herein by reference, and Ausubel et al., (1994-1998, *supra*), in particular Section III of Chapter 11.

In lieu of the polyclonal antisera obtained in the production species, monoclonal antibodies may be produced using the standard method as for example, described in an article by Köhler and Milstein (1975, *Nature* 256, 495-497) which is herein incorporated by reference, or by more recent modifications thereof as for example, described in Coligan et al., (1991, *supra*) by immortalizing spleen or other antibody

producing cells derived from a production species which has been inoculated with one or more of the polypeptides, fragments, variants or derivatives of the invention.

5 The invention also includes within its scope antibodies which comprise Fc or Fab fragments of the polyclonal or monoclonal antibodies referred to above. Alternatively, the antibodies may comprise single chain Fv antibodies (scFvs) against the peptides of
10 the invention. Such scFvs may be prepared, for example, in accordance with the methods described respectively in United States Patent No 5,091,513, European Patent No 239,400 or the article by Winter and Milstein (1991, Nature, 349 293) which are
15 incorporated herein by reference.

 The antibodies of the invention may be used for affinity chromatography in isolating natural or recombinant *N. meningitidis* polypeptides. For example
20 reference may be made to immunoaffinity chromatographic procedures described in Chapter 9.5 of Coligan et al., (1995-1997, *supra*).

 The antibodies can be used to screen expression libraries for variant polypeptides of the invention. The antibodies of the invention can also
25 be used to detect *N. meningitidis* infection described hereinafter.

Detection of *N. meningitidis*

 The presence or absence of *N. meningitidis* in
30 a patient may determined by isolating a biological sample from a patient, mixing an antibody or antibody fragment described above with the biological sample to form a mixture, and detecting specifically bound antibody or bound fragment in the mixture which

indicates the presence of *N. meningitidis* in the sample.

The term "*biological sample*" as used herein refers to a sample which may be extracted, untreated, treated, diluted or concentrated from a patient. Suitably, the biological sample is selected from the group consisting of whole blood, serum, plasma, saliva, urine, sweat, ascitic fluid, peritoneal fluid, synovial fluid, amniotic fluid, cerebrospinal fluid, skin biopsy, and the like.

Any suitable technique for determining formation of the complex may be used. For example, an antibody or antibody fragment according to the invention having a label associated therewith may be utilized in immunoassays. Such immunoassays may include, but are not limited to, radioimmunoassays (RIAs), enzyme-linked immunosorbent assays (ELISAs) and immunochromatographic techniques (ICTs) which are well known those of skill in the art. For example, reference may be made to "CURRENT PROTOCOLS IN IMMUNOLOGY" (1994, *supra*) which discloses a variety of immunoassays that may be used in accordance with the present invention. Immunoassays may include competitive assays as understood in the art.

The label associated with the antibody or antibody fragment may include the following:

- i. direct attachment of the label to the antibody or antibody fragment;
 - ii. indirect attachment of the label to the antibody or antibody fragment; i.e., attachment of the label to another assay reagent which subsequently binds to the antibody or antibody fragment;
- and

iii. attachment to a subsequent reaction product of the antibody or antibody fragment.

5 The label may be selected from a group including a chromogen, a catalyst, an enzyme, a fluorophore, a chemiluminescent molecule, a lanthanide ion such as Europium (Eu^{34}), a radioisotope and a direct visual label.

10 In the case of a direct visual label, use may be made of a colloidal metallic or non-metallic particle, a dye particle, an enzyme or a substrate, an organic polymer, a latex particle, a liposome, or other vesicle containing a signal producing substance and the like.

15 A large number of enzymes suitable for use as labels is disclosed in United States Patent Specifications U.S. 4,366,241, U.S. 4,843,000, and U.S. 4,849,338, all of which are herein incorporated by reference. Suitable enzyme labels useful in the
20 present invention include alkaline phosphatase, horseradish peroxidase, luciferase, β -galactosidase, glucose oxidase, lysozyme, malate dehydrogenase and the like. The enzyme label may be used alone or in combination with a second enzyme which is in solution.

25 Suitably, the fluorophore is selected from a group including fluorescein isothiocyanate (FITC), tetramethylrhodamine isothiocyanate (TRITL) or R-Phycoerythrin (RPE).

30 The invention also extends to a method for detecting infection of patients by *N. meningitidis*, said method comprising the steps of contacting a biological sample from a patient with a polypeptide, fragment, variant or derivative of the invention, and determining the presence or absence of a complex

between said polypeptide, fragment, variant or derivative and *N. meningitidis*-specific antibodies in said serum, wherein the presence of said complex is indicative of said infection.

5 In a preferred embodiment, detection of the above complex is effected by detectably modifying said polypeptide, fragment, variant or derivative with a suitable label as is well known in the art and using such modified compound in a suitable immunoassay as
10 for example described above.

In another aspect, the invention provides a method of detecting *N. meningitidis* bacteria in a biological sample suspected of containing said bacteria, said method comprising the steps of
15 isolating the biological sample from a patient, detecting a nucleic acid sequence according to the invention in said sample which indicates the presence of said bacteria.

Detection of the said nucleic acid sequence
20 may be determined using any suitable technique. For example, a labeled nucleic acid sequence according to the invention may be used as a probe in a Southern blot of a nucleic acid extract obtained from a patient as is well known in the art. Alternatively, a labeled
25 nucleic acid sequence according to the invention may be utilized as a probe in a Northern blot of a RNA extract from the patient. Preferably, a nucleic acid extract from the patient is utilized in concert with oligonucleotide primers corresponding to sense and
30 antisense sequences of a nucleic acid sequence according to the invention, or flanking sequences thereof, in a nucleic acid amplification reaction such as PCR, or the ligase chain reaction (LCR) as for example described in International Application
35 WO89/09385 which is incorporated by reference herein.

A variety of automated solid-phase detection techniques are also appropriate. For example, very large scale immobilized primer arrays (VLSIPS™) are used for the detection of nucleic acids as for example described by Fodor et al., (1991, *Science* 251:767-777) and Kazal et al., (1996, *Nature Medicine* 2:753-759). The above generic techniques are well known to persons skilled in the art.

10 Pharmaceutical compositions

A further feature of the invention is the use of the polypeptide, fragment, variant or derivative of the invention ("immunogenic agents") as actives in a pharmaceutical composition for protecting patients against infection by *N. meningitidis*. Suitably, the pharmaceutical composition comprises a pharmaceutically-acceptable carrier.

By "pharmaceutically-acceptable carrier" is meant a solid or liquid filler, diluent or encapsulating substance which may be safely used in systemic administration. Depending upon the particular route of administration, a variety of pharmaceutically-acceptable carriers, well known in the art may be used. These carriers may be selected from a group including sugars, starches, cellulose and its derivatives, malt, gelatine, talc, calcium sulfate, vegetable oils, synthetic oils, polyols, alginic acid, phosphate buffered solutions, emulsifiers, isotonic saline, and pyrogen-free water.

30 Any suitable route of administration may be employed for providing a patient with the composition of the invention. For example, oral, rectal, parenteral, sublingual, buccal, intravenous, intra-articular, intra-muscular, intra-dermal, subcutaneous,

inhalational, intraocular, intraperitoneal, intracerebroventricular, transdermal and the like may be employed. Intra-muscular and subcutaneous injection is appropriate, for example, for administration of immunogenic compositions, vaccines and DNA vaccines.

Dosage forms include tablets, dispersions, suspensions, injections, solutions, syrups, troches, capsules, suppositories, aerosols, transdermal patches and the like. These dosage forms may also include injecting or implanting controlled releasing devices designed specifically for this purpose or other forms of implants modified to act additionally in this fashion. Controlled release of the therapeutic agent may be effected by coating the same, for example, with hydrophobic polymers including acrylic resins, waxes, higher aliphatic alcohols, polylactic and polyglycolic acids and certain cellulose derivatives such as hydroxypropylmethyl cellulose. In addition, the controlled release may be effected by using other polymer matrices, liposomes and/or microspheres.

Pharmaceutical compositions of the present invention suitable for oral or parenteral administration may be presented as discrete units such as capsules, sachets or tablets each containing a predetermined amount of one or more therapeutic agents of the invention, as a powder or granules or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association one or more immunogenic agents as described above with the carrier which constitutes one or more necessary ingredients. In general, the compositions are

prepared by uniformly and intimately admixing the immunogenic agents of the invention with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the
5 desired presentation.

The above compositions may be administered in a manner compatible with the dosage formulation, and in such amount as is immunogenically-effective to protect patients from *N. meningitidis* infection. The
10 dose administered to a patient, in the context of the present invention, should be sufficient to effect a beneficial response in a patient over time such as a reduction in the level of *N. meningitidis*, or to inhibit infection by *N. meningitidis*. The quantity of
15 the immunogenic agent(s) to be administered may depend on the subject to be treated inclusive of the age, sex, weight and general health condition thereof. In this regard, precise amounts of the immunogenic agent(s) required to be administered will depend on
20 the judgement of the practitioner. In determining the effective amount of the immunogenic agent to be administered in the treatment or prophylaxis against *N. meningitidis*, the physician may evaluate circulating plasma levels, progression of disease, and
25 the production of anti-*N. meningitidis* antibodies. In any event, suitable dosages of the immunogenic agents of the invention may be readily determined by those of skill in the art. Such dosages may be in the order of nanograms to milligrams of the immunogenic agents of
30 the invention.

The above compositions may be used as therapeutic or prophylactic vaccines. Accordingly, the invention extends to the production of vaccines containing as actives one or more of the immunogenic

agents of the invention. Any suitable procedure is contemplated for producing such vaccines. Exemplary procedures include, for example, those described in NEW GENERATION VACCINES (1997, Levine et al., Marcel Dekker, Inc. New York, Basel Hong Kong) which is
5 incorporated herein by reference.

An immunogenic agent according to the invention can be mixed, conjugated or fused with other antigens, including B or T cell epitopes of other
10 antigens. In addition, it can be conjugated to a carrier as described below.

When an haptenic peptide of the invention is used (i.e., a peptide which reacts with cognate antibodies, but cannot itself elicit an immune
15 response), it can be conjugated with an immunogenic carrier. Useful carriers are well known in the art and include for example: thyroglobulin; albumins such as human serum albumin; toxins, toxoids or any mutant crossreactive material (CRM) of the toxin from
20 tetanus, diptheria, pertussis, *Pseudomonas*, *E. coli*, *Staphylococcus*, and *Streptococcus*; polyamino acids such as poly(lysine:glutamic acid); influenza; Rotavirus VP6, Parvovirus VP1 and VP2; hepatitis B virus core protein; hepatitis B virus recombinant
25 vaccine and the like. Alternatively, a fragment or epitope of a carrier protein or other immunogenic protein may be used. For example, a haptenic peptide of the invention can be coupled to a T cell epitope of a bacterial toxin, toxoid or CRM. In this regard,
30 reference may be made to U.S. Patent No 5,785,973 which is incorporated herein by reference.

In addition, a polypeptide, fragment, variant or derivative of the invention may act as a carrier

protein in vaccine compositions directed against *Neisseria*, or against other bacteria or viruses.

The immunogenic agents of the invention may be administered as multivalent subunit vaccines in combination with antigens of *N. meningitidis*, or antigens of other organisms inclusive of the pathogenic bacteria *H. influenzae*, *M. catarrhalis*, *N. gonorrhoeae*, *E. coli*, *S. pneumoniae* etc. Alternatively or additionally, they may be administered in concert with oligosaccharide or polysaccharide components of *N. meningitidis*.

The vaccines can also contain a physiologically-acceptable diluent or excipient such as water, phosphate buffered saline and saline.

The vaccines and immunogenic compositions may include an adjuvant as is well known in the art. Suitable adjuvants include, but are not limited to: surface active substances such as hexadecylamine, octadecylamine, octadecyl amino acid esters, lysolecithin, dimethyldioctadecylammonium bromide, N, N-dioctadecyl-N',N'-bis(2-hydroxyethyl-propanediamine), methoxyhexadecylglycerol, and pluronic polyols; polyamines such as pyran, dextran sulfate, poly IC carbopol; peptides such as muramyl dipeptide and derivatives, dimethylglycine, tuftsin; oil emulsions; and mineral gels such as aluminum phosphate, aluminum hydroxide or alum; lymphokines, QuilA and immune stimulating complexes (ISCOMS).

The immunogenic agents of the invention may be expressed by attenuated viral hosts. By "attenuated viral hosts" is meant viral vectors which are either naturally, or have been rendered, substantially avirulent. A virus may be rendered

substantially avirulent by any suitable physical (e.g., heat treatment) or chemical means (e.g., formaldehyde treatment). By "*substantially avirulent*" is meant a virus whose infectivity has been destroyed. Ideally, the infectivity of the virus is destroyed without affecting the proteins which carry the immunogenicity of the virus. From the foregoing, it will be appreciated that attenuated viral hosts may comprise live viruses or inactivated viruses.

Attenuated viral hosts which may be useful in a vaccine according to the invention may comprise viral vectors inclusive of adenovirus, cytomegalovirus and preferably pox viruses such as vaccinia (see for example Paoletti and Panicali, U.S. Patent No. 4,603,112 which is incorporated herein by reference) and attenuated *Salmonella* strains (see for example Stocker, U.S. Patent No. 4,550,081 which is herein incorporated by reference). Live vaccines are particularly advantageous because they lead to a prolonged stimulus which can confer substantially long-lasting immunity.

Multivalent vaccines can be prepared from one or more microorganisms that express different epitopes of *N. meningitidis* (e.g., other surface proteins or epitopes of *N. meningitidis*). In addition, epitopes of other pathogenic microorganisms can be incorporated into the vaccine.

In a preferred embodiment, this will involve the construction of a recombinant vaccinia virus to express a nucleic acid sequence according to the invention. Upon introduction into a host, the recombinant vaccinia virus expresses the immunogenic agent, and thereby elicits a host CTL response. For example, reference may be made to U.S. Patent No

4,722,848, incorporated herein by reference, which describes vaccinia vectors and methods useful in immunization protocols.

5 A wide variety of other vectors useful for therapeutic administration or immunization with the immunogenic agents of the invention will be apparent to those skilled in the art from the present disclosure.

10 In a further embodiment, the nucleotide sequence may be used as a vaccine in the form of a "naked DNA" vaccine as is known in the art. For example, an expression vector of the invention may be introduced into a mammal, where it causes production of a polypeptide *in vivo*, against which the host
15 mounts an immune response as for example described in Barry, M. *et al.*, (1995, *Nature*, 377:632-635) which is hereby incorporated herein by reference.

Detection kits

20 The present invention also provides kits for the detection of *N. meningitidis* in a biological sample. These will contain one or more particular agents described above depending upon the nature of the test method employed. In this regard, the kits
25 may include one or more of a polypeptide, fragment, variant, derivative, antibody, antibody fragment or nucleic acid according to the invention. The kits may also optionally include appropriate reagents for detection of labels, positive and negative controls,
30 washing solutions, dilution buffers and the like. For example, a nucleic acid-based detection kit may include (i) a nucleic acid according to the invention (which may be used as a positive control), (ii) an oligonucleotide primer according to the invention, and

optionally a DNA polymerase, DNA ligase etc depending on the nucleic acid amplification technique employed.

Preparation of immunoreactive fragments

5 The invention also extends to a method of identifying an immunoreactive fragment of a polypeptide, variant or derivatives according to the invention. This method essentially comprises generating a fragment of the polypeptide, variant or
10 derivative, administering the fragment to a mammal; and detecting an immune response in the mammal. Such response will include production of elements which specifically bind *N. meningitidis* and/or said polypeptide, variant or derivative, and/or a
15 protective effect against *N. meningitidis* infection.

 Prior to testing a particular fragment for immunoreactivity in the above method, a variety of predictive methods may be used to deduce whether a particular fragment can be used to obtain an antibody
20 that cross-reacts with the native antigen. These predictive methods may be based on amino-terminal or carboxy-terminal sequence as for example described in Chapter 11.14 of Ausubel et al., (1994-1998, *supra*). Alternatively, these predictive methods may be based
25 on predictions of hydrophilicity as for example described by Kyte and Doolittle (1982, *J. Mol. Biol.* 157:105-132) and Hopp and Woods (1983, *Mol. Immunol.* 20:483-489) which are incorporated by reference herein, or predictions of secondary structure as for
30 example described by Choo and Fasman (1978, *Ann. Rev. Biochem.* 47:251-276) which is incorporated herein by reference.

 Generally, peptide fragments consisting of 10 to 15 residues provide optimal results. Peptides as

small as 6 or as large as 20 residues have worked successfully. Such peptide fragments may then be chemically coupled to a carrier molecule such as keyhole limpet hemocyanin (KLH) or bovine serum albumin (BSA) as for example described in Sections 11.14 and 11.15 of Ausubel et al., (1994-1998, *supra*).

The peptides may be used to immunize an animal as for example discussed above. Antibody titers against the native or parent polypeptide from which the peptide was selected may then be determined by, for example, radioimmunoassay or ELISA as for instance described in Sections 11.16 and 11.14 of Ausubel et al., (1994-1998, *supra*).

Antibodies may then be purified from a suitable biological fluid of the animal by ammonium sulfate fractionation or by chromatography as is well known in the art. Exemplary protocols for antibody purification is given in Sections 10.11 and 11.13 of Ausubel et al., (1994-1998, *supra*).

Immunoreactivity of the antibody against the native or parent polypeptide may be determined by any suitable procedure such as, for example, western blot.

Functional blockers

The polypeptides according to SEQ ID NOS 2, 5, 7, 9, 11, 13, 15, 17, 19 and 21 are believed to have adhesin properties. They in fact have some similarity to adhesins of *Haemophilus influenzae* which are surface antigens. Specifically they are approximately 67% homologous to the Hia protein of *H. influenzae* (Barenkamp, S. and St. Geme III, J. 1996 *Molecular Microbiology* 19: 1215-1233), and 74% homologous to the Hsf protein of *H. influenzae* (St. Geme III, J. et al, 1996, *Journal of Bacteriology* 178: 6281-6287; and U.S.

Patent No 5,646,259). For these comparisons, a gap weight of 3, and length weight of 0.01 was used using the GAP program (Deveraux, 1984, *supra*). Aligned sequences of these proteins are illustrated in FIG. 6.

5 Thus, interruption of the function of these polypeptides would be of significant therapeutic benefit since they would prevent *N. meningitidis* bacteria from adhering to and invading cells. Interruption of the function may be effected in

10 several ways.

For example, moieties such as chemical reagents or polypeptides which block receptors on the cell surface which interact with a polypeptides according to SEQ ID NOS 2, 5, 7, 9, 11, 13, 15, 17, 19

15 and 21 may be administered. These compete with the infective organism for receptor sites. Such moieties may comprise for example polypeptides of the invention, in particular fragments, or functional equivalents of these as well as mimetics.

20 The term "mimetics" is used herein to refer to chemicals which are designed to resemble particular functional regions of the proteins or peptides. Anti-idiotypic antibodies raised against the above-described antibodies which block the binding of the

25 bacteria to a cell surface may also be used. Alternatively, moieties which interact with the receptor binding sites in the polypeptides according to SEQ ID NO 2, 5, 7, 9, 11, 13, 15, 17, 19 and 21 may effectively prevent infection of a cell by *N.*

30 *meningitidis*. Such moieties may comprise blocking antibodies, peptides or other chemical reagents.

All such moieties, pharmaceutical compositions in which they are combined with pharmaceutically acceptable carriers and methods of

treating patients suffering from *N. meningitidis* infection by administration of such moieties or compositions form a further aspect of the invention.

5 The polypeptides of the invention may be used in the screening of compounds for their use in the above methods. For example, polypeptides of the invention may be combined with a label and exposed to a cell culture in the presence of a reagent under test. The ability of reagent to inhibit the binding
10 of the labeled polypeptide to the cell surface can then be observed. In such a screen, the labeled polypeptides may be used directly on an organism such as *E. coli*. Alternatively, *N. meningitidis* itself may be engineered to express a modified and detectable
15 form of the polypeptide. The use of engineered *N. meningitidis* strains in this method is preferred as it is more likely that the tertiary structure of the protein will resemble more closely that expressed in wild-type bacteria.

20 In order that the invention may be readily understood and put into practical effect, particular preferred embodiments will now be described by way of the following non-limiting examples.

25

EXAMPLE 1

Molecular cloning and subcloning and *hianM* mutant construction.

The *hianM* gene was initially isolated by PCR amplification using standard methods. Briefly, due to
30 our previous work on homologues of the AIDA-I protein of *E. coli* (Jennings, M. et al, 1995, *Microbial Pathogenesis*, 19: 391-407, Peak, I. et al, *Microbial Pathogenesis*, in press) we performed a homology

search, identifying a sequence of interest in preliminary data from the project to sequence the genome of MC5843 (The Institute for Genomic Research, (<ftp://ftp.tigr.org/pub/data/n meningitidis/>) and amplified the region of homology by PCR (polymerase chain reaction) using oligonucleotides A3A (5'-TTTGCAACGGTTCAGGCA-3', SEQ ID NO 28) and A3B (5'-TATTCAGCAGCGTATCGG-3', SEQ ID NO 29). The resulting 449 base pairs (bp) product was cloned into pT7Blue, to create plasmid pNMAIDA3. To clone the full length gene, further oligonucleotides were designed and used in an inverse PCR reaction. These oligonucleotides were A3C (SEQ ID NO 30) and A3D (SEQ ID NO 31) and correspond to the complementary sequence of A3A (SEQ ID NO 28) and A3B (SEQ ID NO 31) respectively. The template for this reaction was chromosomal DNA of MC58 which had been restriction digested with *EagI* and then self ligated. The resulting 3kbp PCR product was cloned into the vector pCRII (Invitrogen), producing plasmid piEagA3. This was digested with *EagI* and *EcoRI* and the resulting fragments of 1.4kbp and 1.6kbp containing cloned DNA were cloned into pBluescriptSKII, M13minus (Stratagene), resulting in piEagA3.8 and piEagA3.9. Plasmid pHiaNm was generated by PCR amplifying *hiaNm* and sequence 5' and 3' to it using oligonucleotide primers HiaNm:P (5'-TTAGATTCCACGTCCCGATT-3', SEQ ID NO 22) and HiaNm:M (5'-CTTCCCTTCAAACCTTCC-3', SEQ ID NO 23), corresponding to nucleotide position (ntp) 113-133 and 2102-2085 respectively of SEQ ID NO 1, and cloning the product into pT7Blue. Plasmid pHiaNmΔKan was created by insertion of a kanamycin resistance cassette into the unique *BglIII* site of pHiaNm corresponding to ntp 680 of SEQ ID No 1. The kanamycin resistance cassette

was excised from pUC4Kan (Pharmacia) with BamHI. pHiaNm Δ Kan was transformed into *N. meningitidis* strain MC58 by incubating bacteria with plasmid DNA for 3 hours on Brain Heart Infusion agar (Acumedia Manufacturer's Inc) supplemented with 10% heated horse blood ("BHI plates") at 37°C in 5% CO₂. A single colony was picked onto fresh selective media, grown, and used for further studies. This mutant strain is designated MC58 Δ HiaNm. Disruption of the *hiaNm* gene in this strain was confirmed by Southern blot using a probe corresponding to ntp 276-2054 of SEQ ID NO 1.

EXAMPLE 2

Nucleotide sequence analysis

Nucleotide sequence analysis was performed using the PRISM Dye terminator sequencing Kit with AmpliTaq DNA polymerase FS or BigDye terminator sequencing kit as suggested by the manufacturer's instructions (Perkin Elmer), in conjunction with a model 373a automated sequencer (Applied Biosystems). For each strain, *hiaNm* was amplified in three independent PCR reactions using primers HiaNm5'A2: 5'-CCAAACCCCGATTAAACC-3' (SEQ ID NO 26) and HiaNm3'A: 5'-AATCGCCACCCTTCCCTTC-3' (SEQ ID NO 27), as indicated on FIG. 1, and corresponding to ntp 230-247 and 2114-2097 of SEQ ID No 1, and the resulting products purified and pooled. This was used as template for direct sequencing on both strands. Data were analysed using the GCG programs (Deveraux et al. (1984) *Nucleic Acids Research* 12, 387-395) and AssemblyLIGN (Oxford Molecular). Several oligonucleotides were generated as necessary to complete sequences. Sequences of *hiaNm* of 10 strains are shown in SEQ ID NOS 1, 3, 4,

6, 8, 10, 12, 14, 16, 18, and 20, and the deduced amino acid sequences of those genes are shown in SEQ ID NO 2, 5, 7, 9, 11, 13, 15, 17, 19 and 21.

Comparison of *hiaNm* from these strains indicated that they share 90-99% identity with *hiaNm* of MC58. In addition, *hiaNm* of MC58 is 62% and 68% homologous to *hia* and *hsf* of *Haemophilus influenzae*. However, in the strains examined, *hiaNm* is 1770-1800 bp long. This is markedly different from the *hia* and *hsf* which are 3294 and 7059 bp long respectively. The predicted polypeptide of *hiaNm*, HiaNm, also exhibits homology to several other bacterial proteins, including AIDA-I, the adhesin involved in diffuse adherence of the diarrhoeagenic *Escherichia coli* strain 2787 (O126:H27), HMW1, another *Haemophilus* adhesin, UspA1, a high molecular weight protein of *Moraxella catarrhalis*, and SepA involved in tissue invasion of *Shigella flexneri* (Benz, I. and Schmidt, M.A., 1992, *Molecular Microbiology* 6:1539-1546, Barenkamp, S.J. and Leininger, E. 1992, *Infection and Immunity* 60: 1302-1313, Aebi, C. et al 1997, *Infection and Immunity* 65: 4367-4377, Benjelloun-Touimi, Z et al 1995, *Molecular Microbiology* 17:123-135). Homology to these (and several other proteins) occurs over the first fifty amino acids of HiaNm. Analysis of this sequence reveals the presence of a predicted signal sequence, with cleavage sites at amino acid 50 in all HiaNm sequences examined. Such long signal sequences are common to proteins located in the outer membrane of Gram-negative bacteria (Henderson, I et al, 1998, *Trends in Microbiology* 6: 370-8). The proteins mentioned above to which the first fifty amino acids of HiaNm is homologous are all members of the "autotransporter" outer-membrane

protein family (Henderson, I, *supra*). This strongly suggests that HiaNm is located in the outer membrane of *N. meningitidis*.

5

EXAMPLE 3Southern blot analysis

Southern blot analysis was performed using standard techniques (Sambrook et al., *supra*, Ausubel et al., *supra*). Briefly, genomic DNA was prepared from 70 strains of *N. meningitidis* of several serogroups, restriction digested and separated electrophoretically on an agarose gel prior to capillary transfer to a nylon membrane. These membranes were hybridized with a labeled probe. The probe used corresponded to ntp 276-2054 of SEQ ID NO 1, encompassing the entire open reading frame of *hiaNm* of strain MC58. This was labeled with DIG (dioxigenin) according to manufacturer's instructions (Boehringer Mannheim). Stringent washes were performed (two washes of 5 minutes at 22°C in 2 x SSC/0.1% SDS followed by two washes of 30 minutes, 68°C, 0.2 x SSC/0.1% SDS). Hybridization was detected colorimetrically using nitro-blue-tetrazolium/ bromo-chloryl-indolyl-phosphate (NBT/BCIP) as recommended by the manufacturer. Signals were detected in all strains examined. (FIG. 2 for example). In addition to the prototypic strain MC58, the following strains were investigated:-

30

TABLE 3

Strain Name	Source	Sero-group	Strain name	Source	Sero-group
PMC 3 (J1079)	2 ^A	A	NGF26	1	B

PMC17 (K874)	2	A	NGG40	1	B
PMC 20 ((H79)	2	A	H15	1	B
PMC23 (K750)	2	A	SWZ107	1	B
PMC 12 (K852)	2	B	528	1	B
PMC 13 (K859)	2	B	2970	1	B
PMC 16 (K873)	2	B	1000	1	B
PMC 24 (K782)	2	B	MPJB28	3 ^c	B
PMC 25 (K791)	2	B	MPJB56	3	B
PMC 27 (K816)	2	B	MPJB88	3	B
PMC 28 (K837)	2	B	MPJB157	3	B
BZ10	1 ^B	B	MPJB328	3	B
BZ47	1	B	MPJB627	3	B
BZ83	1	B	MPJB820	3	B
BZ133	1	E	MPJB945	3	B
BZ147	1	B	PMC 8 (K157)	2	C
BZ163	1	B	PMC 9 (K497)	2	C
BZ169	1	B	PMC 11 (K848)	2	C
BZ198	1	B	PMC 14 (K860)	2	C
BZ232	1	B	PMC 18 (K879)	2	C
NG3/88	1	B	PMC 21 (K656)	2	C
NG4/88	1	B	PMC 29 (K841)	2	C
NG6/88	1	B	MPJC05	3	C
EG327	1	B	MPJC14	3	C
EG329	1	B	MPJC154	3	C
DK353	1	B	MPJC302	3	C
179/82	1	B	MPJC379	3	C
66/84	1	B	PMC19	2	W
DK24	1	B	MPJW025	3	W
NGH36	1	B	PMC 1 (J603)	2	X
H38	1	B	PMC 6 (K131)	2	X
H41	1	B	PMC 10 (K526)	2	Y
NGE28	1	B	PMC 22 (K685)	2	Y
NGE30	1	B	PMC 26 (K810)	2	Y
NGP20	1	B	PMC 2 ((J1049)	2	Z

^A World Health Organization Collaborating Centre for Reference and Research on Meningococci, Oslo, Norway

^B Public Health Laboratory Service Meningococcal

5 Reference Laboratory, Manchester, UK

^c Brisbane Hospitals, now in strain collection of M.P. Jennings, Department of Microbiology, University of Queensland, Brisbane, Australia.

5

EXAMPLE 4Expression and partial purification of MBP-HiaNm

A plasmid vector was constructed which permitted the expression of a protein consisting of a fusion of Maltose Binding Protein and HiaNm (MBP-HiaNm). The plasmid pHiaMBP was generated by amplifying *hiaNm* from MC58 using primers Hianm-MBPA 5'-GGTCGCGGATCCATGAACAAAATATACCGCAT-3' (SEQ ID NO 24) and HiaNm-MBPB 5'-TCACCCAAGCTTAAGCCCTTACCACTGATAAC-3' (SEQ ID NO 25). These primers encompass the start and stop codons of *hiaNm* of *N. meningitidis* strain MC58 and engineered restriction sites for ease of cloning. Plasmid restriction maps and positions of oligonucleotides are shown in FIG. 1. The resultant PCR product was ligated into *Bam*HI/*Hind*III restriction digested plasmid pMALC2 (New England Biolabs), and the resultant plasmid, pHiaMBP (See FIG. 1) reintroduced to *E. coli* strain DH5 α . This *E. coli* strain containing pHiaMBP was induced to express the HiaNm-MBP fusion protein under conditions recommended by the manufacturer (New England Biolabs). Cell extracts from cultures containing pHiaMBP were separated by 10% SDS-PAGE, and the fusion protein was partially purified by elution using the Mini-Gel Electro-eluter (BioRad) according to manufacturer's instructions. Fractions containing the HiaNm-MBP fusion protein were detected by Western blot using rabbit anti-MBP sera (New England Biolabs). The purity of the HiaNm-MBP

fusion protein was determined by SDS-PAGE followed by Coomassie staining, and the amount of recovered protein estimated by BCA assay (Sigma) or absorbance at a wavelength of 280nm.

5

EXAMPLE 5

Generation of polyclonal sera

The partially purified HiaNm-MBP fusion protein obtained in Example 4 was used to generate polyclonal sera in rabbits. Samples of eluted HiaNmMBP fusion protein were dialyzed against sterile phosphate buffered saline pH 7.4, (PBS) (Sigma). This was then mixed with adjuvant (MPL+TDM+CWS, Sigma), at a concentration of 50-150µg/mL and inoculated at two weekly intervals into two New Zealand White rabbits. Blood was taken from these rabbits. Serum was extracted by clotting at room temperature for one hour followed by overnight incubation at 4°C before centrifugation at 4000 x rpm at 4°C. The supernatant was removed and re-centrifuged. Serum was stored in aliquots at -80°C. Sera obtained were used in bactericidal assays and Western blots (see below).

To test the specificity of the sera obtained, Western blot analysis was undertaken. Briefly, proteins of *N. meningitidis* strains MC58 and MC58ΔHianm were separated electrophoretically on SDS-PAGE before electrophoretic transfer to nitrocellulose membrane using a Semi-Dry Blotter (BioRad). These were then incubated sequentially with sera and alkaline-phosphatase conjugated anti-Rabbit IgG (Sigma) before colorimetric detection with NBT/BCIP (Sigma). These experiments demonstrated that antibodies were elicited by the HiaNm-MBP fusion protein which

were specific for, and detected a band in, MC58 but not in MC58 Δ HiaNm (see FIG. 4). The predicted molecular weight of the deduced polypeptide of HiaNm is 62.3 kDa. The band detected by the sera migrates at an apparent MW in excess of 150 kDa. At least three of the homologous "autotransporter" proteins reported in the literature also display such anomalous migration: the high molecular weight outer membrane proteins UspA1 and UspA2 of *Moraxella catarrhalis* have predicted molecular weights of 62.5 kDa and 88.3 kDa respectively but migrate at 85 kDa and 120 kDa, respectively and as the UspA complex at between 350 kDa and 720 kDa (Aebi, C. et al., 1997, *Infection and Immunity*, 65: 4367-4377, Klingman, K.L. and Murphy, T.F., 1994, *Infection and Immunity*, 62: 1150-1155). Similarly, Hia of *Haemophilus influenzae* has a predicted molecular weight of 116 kDa but when expressed in a phage, Hia migrates at greater than 200 kDa (Barenkamp, S. and St. Geme III, J. 1996 *Molecular Microbiology* 19: 1215-1233).

In order to confirm that HiaNm is associated with the outer membrane of *N. meningitidis*, outer membrane complexes (omc) were prepared, essentially as previously described (van der Ley, P. et al, 1991, *Infection and Immunity*, 59:2963-71). Briefly, bacteria were grown overnight on Brain Heart Infusion agar (Acumedia Manufacturer's Inc) supplemented with 10% heated horse blood BHI plates, resuspended in 10 mM Tris pH 8.0 and heat killed, before sonication to disrupt the membrane. Cellular debris were removed by centrifugation at 10,000 x g (rcf, relative centrifugal force), and the supernatant recentrifuged at 50,000 x g. This pellet was resuspended in 1% sarkosyl/10 mM Tris pH8.4 and centrifuged at 10,000 x

g. The supernatant was centrifuged at 75,000 x g and the pellet resuspended in Tris pH 8.4, before quantification spectrophotometrically at a wavelength of 280nm. An aliquot of the sarkosyl-insoluble fraction, which contains outer membrane proteins, (50 μ l of A_{280} =3.75) was subjected to SDS-PAGE and Western blotted as described above. The results, shown in FIG. 4 demonstrate that reactivity with the anti-HiaNmMBP antisera is observed with wild type MC58, but not with MC58 Δ HiaNm, in which *hianm* has been inactivated. The increase in reactivity with the anti-HiaMBP sera observed between whole cell samples, and the omc samples containing the same amount of total protein, in MC58 cultures is consistent with the membrane association of HiaNm.

EXAMPLE 6

Bactericidal assay

To determine whether the anti-HiaMBP antisera contained bactericidal antibodies specific for HiaNm, bactericidal assays were performed with wild type MC58 and MC58 Δ HiaNm. This assay was performed by a modification of the method described by Hoogerhout et. al. (1995, *Infection and Immunity*, 63: 3473-3478). Briefly, MC58 and MC58 Δ HiaNm were grown overnight on BHI plates at 37°C in 5% CO₂. Bacteria from this overnight culture were subcultured under the same conditions for 4-6 hours before suspension in 1 mL PBS. Numbers of bacteria were estimated by lysis of a sample in 0.2N NaOH/1% SDS and absorbance at a wavelength of 260 nm, where $A_{260}=1 = 10^9$ cfu/mL. The bacterial suspension was adjusted to approximately 10^5 cfu/mL in PBS. Rabbit sera to be tested was heat

inactivated at 56°C for 45 minutes. Serum from four week old, New Zealand White rabbits was pooled and used as a source of complement (Central Animal Breeding House, University of Queensland). The assay was carried out in sterile polystyrene flat-bottomed 96 well microtitre plate. The total volume in each well was 24 µL: 12 µL of twofold serially diluted serum in PBS and 6 µL of bacterial suspension (containing between 300-900 bacteria). Sera and bacteria were incubated at room temperature for 10 minutes before addition of 6 µL of 80% complement in PBS (final concentration 20% vol/vol). Controls were a) PBS, bacteria and complement, b) PBS, bacteria and serum. After addition of all components and mixing, a 7 µL aliquot from each control well was spread on a BHI plate. The microtitre plate was then incubated at 37°C in 5% CO₂ for 60 minutes. After this incubation, a 7 µL aliquot from each well was spread on BHI plates. All BHI plates were then incubated for 14-18 hours at 37°C in 5% CO₂, and bacterial colonies counted. Serum bactericidal killing is reported as the highest reciprocal dilution at which at least 90% of bacteria were killed. Serum used was from the same rabbit and the same test bleed as used for Western blot experiments as reported in Example 5 above. These experiments consistently demonstrated reduced titers (approximately 3 fold, Table 4) of killing against MC58ΔHiaNm in comparison to the wild type strain, MC58, indicating that the anti-HiaMBP antisera contained bactericidal antibodies specific for HiaNm.

TABLE 4

STRAIN	TITRE ^a
--------	--------------------

MC58	12 (+/- 4.6)
MC58 Δ HiaNm	3.5 (+/- 1)

^a Mean of four independent experiments

DISCUSSION

5 Repetitive DNA has been associated with
virulence determinants in some pathogenic bacteria.
Southern blots using such a repetitive DNA motif
revealed the presence of at least three loci which
10 contained this motif in *N. meningitidis* strain MC58
(Peak, I. et al., 1996, *FEMS Microbiology Letters*,
137:109-114). These genes were cloned and sequence
analysis of two of these repeat associated loci
(nmrep2 and nmrep3) revealed open reading frames of
approximately 670 amino acids (Jennings, M. et al,
15 1995, *Microbial Pathogenesis*, 19: 391-407, Peak, I. et
al, *Microbial Pathogenesis*, in press). These
exhibited homology to each other and homology to the
carboxyl-terminal of the adhesin AIDA-I of *E. coli*.
AIDA-I is 1286 amino acids long. The carboxyl-
20 terminal region constitutes a putative outer membrane
transport domain and the amino-terminal domain of the
mature protein constitutes the adhesin domain. The
amino-terminal domain crosses the membrane through the
putative transport domain and is designated the
25 passenger domain.

As Nmep2 and Nmep3 share sequence homology
with the transporter domain of AIDA-I, they are
thought to form membrane pores. Nmrep2 and Nmrep3 are
approximately half the size of AIDA-I, and are
30 homologous to the membrane spanning domain of AIDA-I.
We hypothesized that there existed in *N. meningitidis*

a locus with homology to the amino-terminal domain of AIDA-I. We searched for such a homologue in the data from the project to sequence *N. meningitidis* strain MC58 ϕ 3 (TIGR, *supra*) and found one region with
5 homology to a gene designated AIDA-I in *Haemophilus influenzae* strain Rd (HI1732) because of its homology to AIDA-I of *E. coli*, (Fleischmann et. al., 1995 *Science* 269:496-512,). In view of the homologies noted above, the applicants decided to investigate further.

10 The gene was initially isolated by PCR amplification of the DNA corresponding to the 471 base pair fragment, named gnmaa84r, from *N. meningitidis* MC58 3 and the sequence was confirmed. Further PCR experiments enabled larger fragments to be amplified.
15 These were cloned and sequence analysis undertaken as shown in FIG 1. The gene exhibited homology to the amino-terminal region of AIDA-I of *E. coli* and we designated it *aida3*, as it represented the third AIDA-I homologue in *N. meningitidis* (with *nmrep2* and
20 *nmrep3*). Since then, the discovery of two further genes, *hia* and *hsf* from *H. influenzae* has been published (Barenkamp, S. and St. Geme III, J. 1996 *Molecular Microbiology* 19: 1215-1233, St. Geme III, J. et al, 1996, *Journal of Bacteriology* 178: 6281-6287),
25 to which *aida3* is more similar. We have therefore re-designated this gene *hiaNm*. (HI1732, the *H. influenzae* gene first identified as an homologue of AIDA-I has also been re-designated *hia* in light of the reports of Barenkamp and St. Geme III).

30 Throughout the specification the aim has been to describe the preferred embodiments of the invention without limiting the invention to any one embodiment or specific collection of features. It will therefore

be appreciated by those of skill in the art that, in light of the instant disclosure, various modifications and changes can be made in the particular embodiments exemplified without departing from the scope of the present invention. All such modifications and changes are intended to be included within the scope of the appendant claims

CLAIMS

1. An isolated polypeptide or fragment thereof, or variant or derivative of these, said polypeptide selected from the group consisting of:

- 5 (a) a polypeptide according to SEQ ID NO 2;
(b) a polypeptide according to SEQ ID NO 5;
(c) a polypeptide according to SEQ ID NO 7;
(d) a polypeptide according to SEQ ID NO 9;
(e) a polypeptide according to SEQ ID NO 11;
10 (f) a polypeptide according to SEQ ID NO 13;
(g) a polypeptide according to SEQ ID NO 15;
(h) a polypeptide according to SEQ ID NO 17;
(i) a polypeptide according to SEQ ID NO 19;
and
15 (j) a polypeptide according to SEQ ID NO 21.

2. A polypeptide, fragment, variant or derivative according to claim 1, displaying immunological activity against one or more members selected from the group consisting of:-

- 20 (i) *N. meningitidis*;
(ii) said polypeptide;
(iii) said fragment;
(iv) said variant; and
25 (v) said derivative;

3. A polypeptide, fragment, variant or derivative according to claim 1, displaying immunological activity against *N. meningitidis*.

30

4. An isolated nucleic acid sequence encoding a polypeptide or fragment thereof, or variant or derivative of these, said polypeptide selected from the group consisting of:

- 5 (a) a polypeptide according to SEQ ID NO 2;
(b) a polypeptide according to SEQ ID NO 5;
(c) a polypeptide according to SEQ ID NO 7;
(d) a polypeptide according to SEQ ID NO 9;
(e) a polypeptide according to SEQ ID NO 11;
(f) a polypeptide according to SEQ ID NO 13;
(g) a polypeptide according to SEQ ID NO 15;
(h) a polypeptide according to SEQ ID NO 17;
(i) a polypeptide according to SEQ ID NO 19;
10 and
(j) a polypeptide according to SEQ ID NO 21.

5. An isolated nucleic acid sequence according to claim 4, encoding a product displaying immunological activity against one or more members selected from the group consisting of:-

- 15 (i) *N. meningitidis*;
(ii) said polypeptide;
(iii) said fragment;
20 (iv) said variant; and
(v) said derivative.

6. An isolated nucleic acid sequence according to claim 4, encoding a product displaying immunological activity against *N. meningitidis*.

7. An isolated nucleic acid sequence selected from the group consisting of:

- 30 (1) the nucleotide sequence of SEQ ID NO 1;
(2) the nucleotide sequence of SEQ ID NO 3;
(3) the nucleotide sequence of SEQ ID NO 4;
(4) the nucleotide sequence of SEQ ID NO 6;
(5) the nucleotide sequence of SEQ ID NO 8;
(6) the nucleotide sequence of SEQ ID NO 10;
35 (7) the nucleotide sequence of SEQ ID NO 12;

- 5 (8) the nucleotide sequence of SEQ ID NO 14;
(9) the nucleotide sequence of SEQ ID NO 16;
(10) the nucleotide sequence of SEQ ID NO 18;
(11) the nucleotide sequence of SEQ ID NO 20;
(12) a nucleotide sequence fragment of any
one of SEQ ID NOS 1, 3, 4, 6, 8, 10, 12,
14, 16, 18 and 20; and
(13) a nucleotide sequence homologue of any
of the foregoing sequences

10

8. A nucleic acid sequence according to claim 7,
encoding a product displaying immunological activity
against one or more members selected from the group
consisting of:-

- 15 (i) *N. meningitidis*;
(ii) said polypeptide;
(iii) said fragment;
(iv) said variant; and
(v) said derivative.

20

9. A nucleic acid sequence according to claim 7,
encoding a product displaying immunological activity
against *N. meningitidis*.

25 10. The nucleic acid sequence of claim 7, wherein
said homologue is obtained from the genus *Neisseria*.

11. The nucleic acid sequence of claim 5 or claim
7, wherein said homologue is obtained from a strain of
30 *N. meningitidis*.

12. A method of obtaining a nucleotide sequence
homologue comprising the steps of:-

- 35 (i) obtaining a nucleic acid extract from
a suitable host;

- (ii) creating primers which are optionally degenerate wherein each comprises a portion of a nucleic acid sequence according to claim 5 or claim 7; and
- 5 (iii) using said primers to amplify, via a nucleic acid amplification technique, one or more amplification products from said nucleic acid extract.

10 13. The method of claim 12, wherein said nucleic acid extract is obtained from the genus *Neisseria*.

14. The method of claim 12, wherein said nucleic acid extract is obtained from a strain of *N. meningitidis*.

15

15. The method of claim 12, wherein said primers are selected from the group consisting of SEQ ID NOS 22, 23, 24, 25, 26, 27, 28, 29, 30, and 31.

20

16. The method of claim 12, wherein the nucleic acid amplification technique is PCR.

17. An expression vector comprising a nucleic acid sequence according to claim 4 or claim 7, wherein said sequence is operably linked to transcriptional and translational regulatory nucleic acid.

25

18. A host cell transfected or transformed with an expression vector comprising a nucleic acid sequence according to claim 4 or claim 7, wherein said sequence is operably linked to transcriptional and translational regulatory nucleic acid.

30

19. A method of producing a recombinant polypeptide comprising the steps of:

- 5 (A) culturing a host cell according to claim 18 such that said recombinant polypeptide is expressed from said nucleic acid; and
(B) isolating said recombinant polypeptide.

20. An antibody or antibody fragment which binds
10 to one or more members selected from the group consisting of:-

- (1) *N. meningitidis*;
(2) a polypeptide according to claim 1;
(3) a fragment of said polypeptide;
15 (4) a variant of said polypeptide or said fragment; and
(5) a derivative of said polypeptide or said fragment.

20 21. The antibody of claim 20, wherein said antibody or antibody fragment binds *N. meningitidis*.

22. A method of detecting *N. meningitidis* in a biological sample suspected of containing same, said
25 method comprising the steps of:-

- (A) isolating the biological sample from a patient;
(B) mixing the antibody or antibody fragment
30 of claim 20 or claim 21 with the biological sample to form a mixture; and
(C) detecting specifically bound antibody or bound fragment in the mixture which indicates the presence of *N. meningitidis*.

23. A method of detecting *N. meningitidis* bacteria in a biological sample suspected of containing said bacteria, said method comprising the steps of:-

- (I) isolating the biological sample from a patient;
- (II) detecting a nucleic acid sequence according to claim 4 or claim 7 in said sample which indicates the presence of said bacteria.

24. A method for diagnosing infection of patients by *N. meningitidis*, said method comprising the steps of:-

- (1) contacting a biological sample from a patient with a polypeptide, fragment, variant or derivative according to claim 1; and
- (2) determining the presence or absence of a complex between said polypeptide, fragment, variant or derivative and *N. meningitidis*-specific antibodies in said sample, wherein the presence of said complex is indicative of said infection.

25. Use of the polypeptide, fragment, variant or derivative according to claim 1 for the manufacture of a kit for the detection or diagnosis of *N. meningitidis* infection in humans.

26. Use of the nucleic acid sequence according to claim 4 or claim 7 for the manufacture of a kit for

the detection or diagnosis of *N. meningitidis* infection in humans.

27. Use of one or more oligonucleotide primers
5 selected from the group consisting of SEQ ID NOS 22, 23, 24, 25, 26, 27, 28, 29, 30 and 31, and optionally a thermostable polymerase, in a kit for the detection or diagnosis of *N. meningitidis* infection in humans.

10 28. Use of the antibody or antibody fragment according to claim 20 or claim 21 for the manufacture of a kit for the detection or diagnosis of *N. meningitidis* infection in humans.

15 29. Use of a pharmaceutically effective amount of a polypeptide, fragment, variant or derivative according to claim 1 for the prevention or treatment of *N. meningitidis* infection in humans.

20 30. Use of a pharmaceutically effective amount of an antibody or antibody fragment according to claim 20 or claim 21 for the prevention or treatment of *N. meningitidis* infection in humans.

25 31. A pharmaceutical composition comprising an isolated polypeptide or fragment thereof, or a variant or derivative of these, according to claim 1.

30 32. The pharmaceutical of claim 31, which is a vaccine.

33. A method of preventing or treating infection of a patient by *N. meningitidis*, comprising the step

of administering a pharmaceutically effective amount of a vaccine according to claim 32.

34. A method of identifying an immunoreactive
5 fragment of a polypeptide, variant or derivatives according to claim 1, comprising the steps of:-

(a) generating a fragment of said
polypeptide, variant or derivative;
(b) administering said fragment to a
10 mammal; and

detecting an immune response in said mammal
which response includes production of elements which
specifically bind *N. meningitidis* and/or said
polypeptide, variant or derivative, and/or a
15 protective effect against *N. meningitidis* infection.

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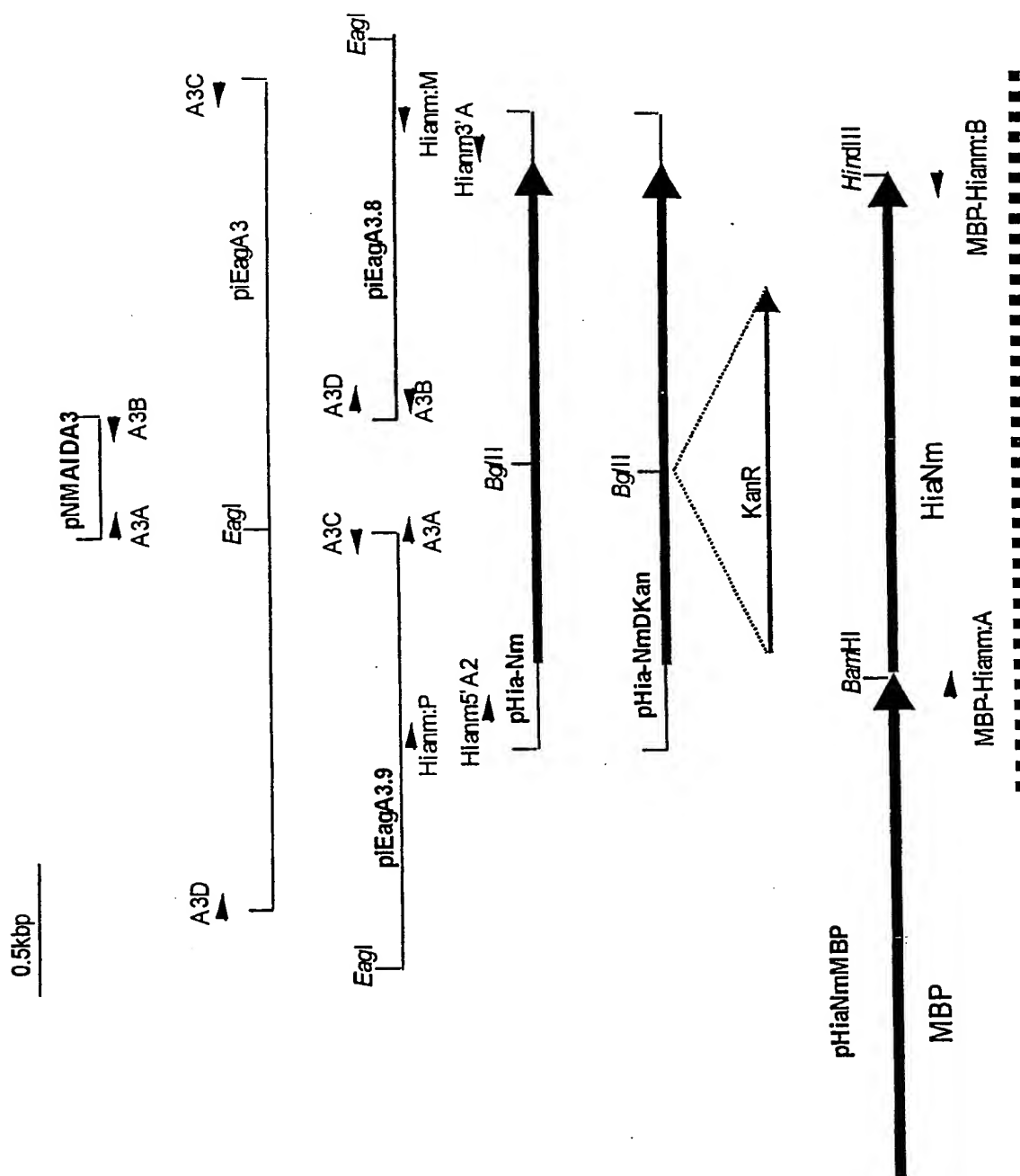


FIG. 1

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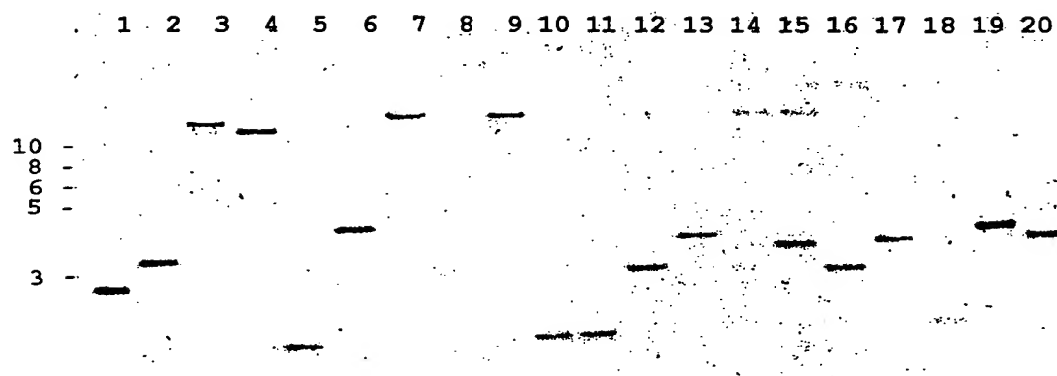


FIG. 2A

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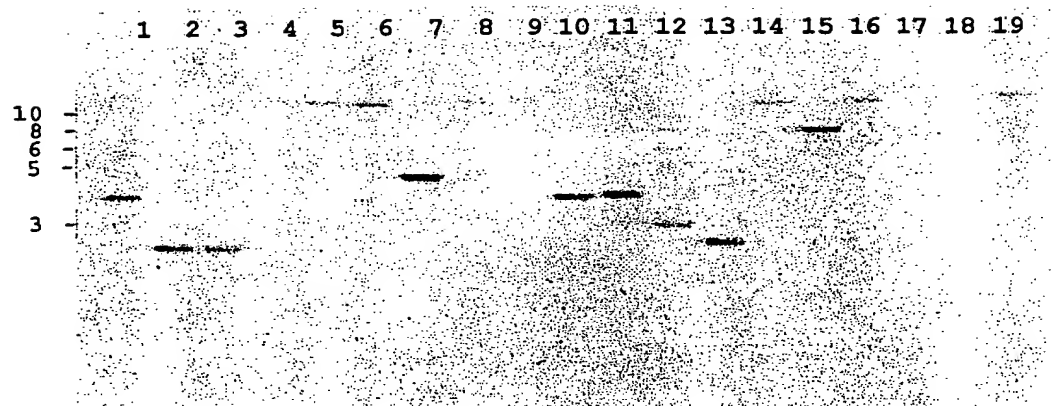


FIG. 2B

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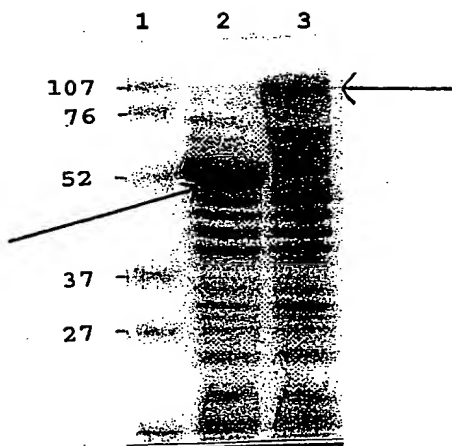


FIG. 3

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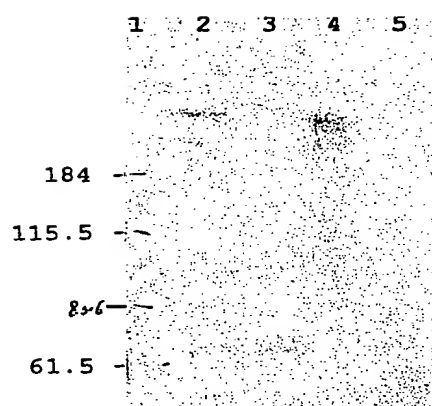


FIG. 4

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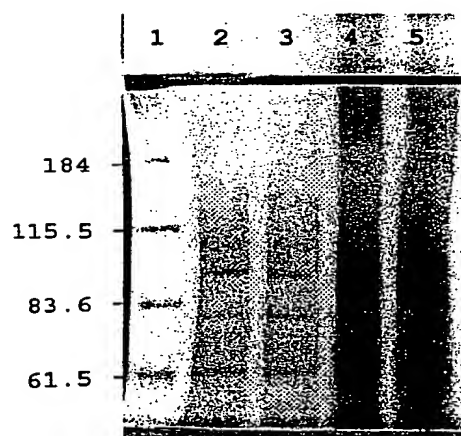


FIG. 5

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FIG. 6

	1				50
Hsf	MNKIFNVIWN	VMTQTWVVVS	ELTRTHTKRA	SATVETAVLA	TLLFATVQAN
Hia	MNKIFNVIWN	VVTQTWVVVS	ELTRTHTKCA	SATVAVAVLA	TLLSATVEAN
HiaNm	MNKIYRIIWN	SALNAWVVVS	ELTRNHTKRA	SATVKTAVLA	TLLFATVQAS
	51				100
Hsf	ATDEDEELDP	VVRTAPVLSF	HSDKEGTGEK	EVTENSNWGI	YFDNKGVLKA
Hia
HiaNm	A.....
	101				150
Hsf	GAITLKAGDN	LKIKQNTDES	TNASSFTYSL	KKDLTDLTSV	ATEKLSFGAN
Hia
HiaNm
	151				200
Hsf	GDKVDITSDA	NGLKLAKTGN	GNVHLNGLDS	TLPDAVTNTG	VLSSSSFTPN
HiaNNTP	V.....
HiaNm
	201				250
Hsf	DVEKTRAATV	KDVLNAGWNI	KGAKTAGGNV	ESVDLVSAYN	NVEFITGDKN
Hia
HiaNm
	251				300
Hsf	TLDVVLTAKE	NGKTTEVKFT	PKTSVIKEKD	GKLFTGKENN	DTNKVTSNTA
HiaTNK.....
HiaNm
	301				350
Hsf	TDNTDEGNGL	VTAKAVIDAV	NKAGWRVKTT	TANGQNGDFA	TVASGTNVTF
Hia
HiaNm
	351				400
Hsf	ESGDGTTASV	TKDTNGNGIT	VKYDAKVG DG	LKFDSDDKKIV	ADTTALTVTG
Hia
HiaNm
	401				450
Hsf	GKVAEIAKED	DKKKLVNAGD	LVTALGNLSW	KAKAEADTDG	ALEGISKDQE
Hia
HiaNm
	451				500
Hsf	VKAGETVTFK	AGKNLKVQD	GANFTYSLQD	ALTGLTSITL	GGTTNGGND
Hia
HiaNm
	501				550
Hsf	KTVINKDGLT	ITPAGNGGTT	GTNTISVTKD	GIKAGNKAIT	NVASGLRAYD
HiaLKAYG
HiaNm

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FIG. 6 cont'd

	551				600
Hsf	DANFDVLNNS	ATDLNRHVED	AYKGLLNLNE	KNANKQPLVT	DSTAATVGD
Hia	DANFNFTNNS	IADA EKQVQE	AYKGLLNLNE	KNASDKLLVE	DNTAATVGNL
HiaNmNN	ERPRKKDLYL	DPVQRTVAVL
	601				650
Hsf	RKLGWVSTK	NGTKEE.SNQ	VKQAD.EVLF	TGAGAATVTS	KSENGKHTIT
Hia	RKLGWVLSSK	NGTRNEKSQQ	VKHAD.EVLF	EGKGGVQVTS	TSENGKHT..
HiaNm	I....VNSDK	EGT.GEKEKV	EENS DWAVYF	NEKGVLT...
	651				700
Hsf	VSV AETKADC	GLEKDGDTIK	LKVDNQNTDN	VLTVGNNGTA	VTKGGFETVK
Hia
HiaNm
	701				750
Hsf	TGATDADRGK	VTVKDATAND	ADKKVATVKD	VATAINSAAT	FVKTENLTTS
Hia
HiaNm
	751				800
Hsf	IDEDNPTDNG	KDDALKAGDT	LTFKAGKNLK	VKRDGKNITF	DLAKNLEVKT
HiaITF	ALAKDLGVKT
HiaNmARE	ITLKAGDNLK	IKQNGTNFTY	SLKKDLTDLT
	801				850
Hsf	AKVSDTLTIG	GNTPTGGTTA	TPKVNITSTA	DGLNFAKETA	DASGSKNVYL
Hia	ATVSDTLTIG	GGAAAGATT.	TPKVNVTSTT	DGLKFAKDAA	GANG.....
HiaNm	SVGTEKLSFS	ANGN.....	..KVNITSDT	KGLNFAKETA	GTNG.....
	851				900
Hsf	KGIATTLTEP	SAGAKSSHVD	LNVDATKKS	AASIEDVLRA	GWNIQGNNGN
Hia
HiaNm
	901				950
Hsf	VDYVATYDTV	NFTDDSTGTT	TVT VTQKADG	KGADV KIGAK	TSVIKDHNGK
Hia
HiaNm
	951				1000
Hsf	LFTGKDLKDA	NNGATVSEDD	GKDTGTGLVT	AKTVIDAVNK	SGWRVTGEGA
Hia
HiaNm
	1001				1050
Hsf	TAETGATAVN	AGNAETVTSG	TSVNFKNGNA	TTATVSKDNG	NINV KYDVNV
Hia
HiaNm
	1051				1100
Hsf	GDGLKIGDDK	KIVADTTTLT	VTGGKVS VPA	GANSVNNNKK	LVNAEGLATA
HiaDTT...
HiaNmDTT...

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FIG. 6 cont'd

	1101		1150
Hsf	LNNLSWTAKA	DKYADGESEG	ETDQEVKAGD KVTFKAGKNL KVKQSEKDFT
Hia
HiaNm
	1151		1200
Hsf	YSLQDTLTGL	TSITLGGTAN	GRNDTGTVIN KDGLTITLAN GAAAGTDASN
Hia
HiaNm
	1201		1250
Hsf	GNTISVTKDG	ISAGNKEITN	VKSALKTYKD TQNTADETQD KEFHAAVKNA
Hia
HiaNm
	1251		1300
Hsf	NEVEFVGKNG	ATVSAKTDNN	GKHTVTIDVA EAKVG DGLEK DTDGKIKLKV
Hia
HiaNm
	1301		1350
Hsf	DNTDGNLLT	VDA TKGASVA	KGEFNAVTTD ATTAQGTNAN ERGKVVVKGS
Hia
HiaNm
	1351		1400
Hsf	NGATATETDK	KKVATVGDVA	KAINDAATFV KVENDDSATI DDSPTDDGAN
Hia
HiaNm
	1401		1450
Hsf	DALKAGDTLT	LKAGKNLKVK	RDGKNITFAL ANDLSVKSAT VSDKLSLGTN
Hia
HiaNm
	1451		1500
Hsf	GNKVNITS DT	KGLNFAKDSK	TGDDANIHLN GIASTLTDTL LNSGATTNLG
HiaVHLN GIGSTLTDTL VGSPATHIDG
HiaNmVHLN GIGSTLTDTL LNTGATTNVT
	1501		1550
Hsf	GNGITDNEKK	RAASVKDVLN	AGWNVRGV KP ASANNQVENI DFVATYDTVD
Hia	GDQSTHY..T	RAASIKDVLN	AGWNIKG VKA GSTTGQSENV DFVHTYDTVE
HiaNm	NDNVT DDEKK	RAASVKDVLN	AGWNIKG VKP GTTA..SDNV DFVRTYDTVE
	1551		1600
Hsf	FVSGDKDTTS	VTVESKDNGK	RTEVKIGAKT SVIKDHNGKL FTGKELK DAN
Hia	FLSADTETTT	VTVD SKENGK	RTEVKIGAKT SVIKEKDGKL FTGKANKETN
HiaNm	FLSADTKTTT	VNVESKDNGK	KTEVKIGVKT SVIKEKDGKL VTGKD.KGEN
	1601		1650
Hsf	NNGVTVTETD	GKDEGNGLVT	AKAVIDAVNK AGWRVKT TGA NGQNDD...F
Hia	KVD.GANATE	DADEGKGLVT	AKDVIDAVNK TGWRIKT TDA NGQNGD...F
HiaNmGS	STDEGEGLVT	AKEVIDAVNK AGWRMKT TTA NGQTGQADKF

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FIG. 6 cont'd

	1651				1700
Hsf	ATVASGNTVT	FADGNGTTAE	VTKANDGSIT	VKYNVKVADG	LKLDGDKIVA
Hia	ATVASGNTVT	FASGNGTTAT	VTNGTDG.IT	VKYDAKVG DG	LKLDGDKIAA
HiaNm	ETVTSGNTVT	FASGKGTTAT	VSKDDQGNIT	VMYDVNVGDA	LNVNQ.....
	1701				1750
Hsf	DTTVLTVAD.GKV	TAPNNGDGKK	FVDASGLADA	LNKLSWTATA
Hia	DTTALTVDNG	KNANNPKGKV	ADVASTDEKK	LVTAKGLVTA	LNSLSWTTTA
HiaNmLQNSGW...	..NLDSKAVA
	1751				1800
Hsf	GKEGTGEVDP	ANSAGQEVKA	GDKVTFKAGD	NLKI KQSGKD	FTYSLKKELK
Hia	AEADGGTLD.	GNASEQEVKA	GDKVTFKAGK	NLKV KQEGAN	FTYSLQDALT
HiaNm	G..SSGKVIS	GNVSPSKGKM	DETVNINAGN	NIEITRNGKN	I..DIATSMT
	1801				1850
Hsf	.DLTSVEFKD	ANGGTGSEST	KITKDGLTIT	PANGAGAAGA	NTANTISVTK
Hia	.GLTSITLGT	GNGA...KT	EINKDGLTIT	PANG...AGA	NNANTISVTK
HiaNm	PQFSSVSLG.AGA	D.APTLSV..
	1851				1900
Hsf	DGISAGNKAV	TNVVSGLK KF	GDGHTLANGT	VAD.FEKHYD	NAYKDLTNLD
Hia	DGISAGGQSV	KNVVSGLK KF	GDANFDPLTS	SADNLTKQND	DAYKGLTNLD
HiaNm
	1901				1950
Hsf	EKGADNN.PT	VADNTAATVG	DLRGLGWVIS	ADKTTGEPNQ	EYNAQVRNAN
Hia	EKGTDKQTPV	VADNTAATVG	DLRGLGWVIS	ADKTTGGST.	EYHDQVRNAN
HiaNm
	1951				2000
Hsf	EVKFKSGNGI	NVSGKTLNGT	RVITFELAKG	EVVKSNEFTV	KNADGSETNL
Hia	EVKFKSGNGI	NVSGKTVNGR	REITFELAKG	EVVKSNEFTV	KETNGKETS L
HiaNmDGDAL	NVGSK.....
	2001				2050
Hsf	VKVGDMYYSK	EDIDPATSKP	..MTGKT..E	KYKVENGKV V	SANGSKTEVT
Hia	VKVGDKYYSK	EDIDLTTGQP	KLKDGNTVAA	KYQDKGGKV V	SVTD.NTEAT
HiaNmKDNKP V	R.....
	2051				2100
Hsf	LTNKGSGYVT	GNQVADAI AK	SGFELGLADA	AEA EKAF AES	AKDKQLSKDK
Hia	ITNKGSGYVT	GNQVADAI AK	SGFELGLADE	ADAKRAFDD.	.KTKALSAGT
HiaNm	ITNVAPG...
	2101				2150
Hsf	AETVNAHDKV	RFANGLNTKV	SAATVESTDA	NGDKVTTTFV	KTDVELPLTQ
Hia	TEIVNAHDKV	RFANGLNTKV	SAATVESTDA	NGDKVTTTFV	KTDVELPLTQ
HiaNm
	2151				2200
Hsf	IYNTDANGNK	I...VKKADG	KWYELNADGT	AS.NKEVTLG	NVDANGKKV V
Hia	IYNTDANGKK	ITKVVKDGQT	KWYELNADGT	ADMTKEVTLG	NVDS DGKKV V
HiaNmVKEGD.

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FIG. 6 cont'd

2201 2250
 Hsf KVTENGADKW YYTNADGAAD KTKGEVSNDK VSTDEKHVVR LDPNNQSNKG
 Hia K...DNDGKW YHAKADGTAD KTKGEVSNDK VSTDEKHVVS LDPNDQSKGK
 HiaNm

2251 2300
 Hsf GVVIDNVANG EISATSTDAI NGSQLYAVAK GVTNLAGQVN NLEGKVNKVG
 Hia GVVIDNVANG DISATSTDAI NGSQLYAVAK GVTNLAGQVN NLEGKVNKVG
 HiaNm ...VTNVA... ..QLKGVA.Q NLNNRIDNVD

2301 2350
 Hsf KRADAGTASA LAASQLPQAT MPGKSMVAIA GSSYQGQNGL AIGVSRISDN
 Hia KRADAGTASA LAASQLPQAT MPGKSMVAIA GSSYQGQNGL AIGVSRISDN
 HiaNm GNARAGIAQA IATAGLVQAY LPGKSMAIG GGTyrGEAGY AIGYSSISDG

2351 2378
 Hsf GKVIIRLSGT TNSQGKTGVA AGVGYQW*
 Hia GKVIIRLSGT TNSQGKTGVA AGVGYQW*
 HiaNm GNWIIGKTAS GNSRGHFGAS ASVGYQW*

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FIG. 7

	1				50
eg329	MNEILRIIWN	SALNAWVVVS	ELTRNHTKRA	SATVKTAVLA	TLLFATVQAS
pmc21	MNKIYRIIWN	SALNAWVVVS	ELTRNHTKRA	SATVKTAVLA	TLLFATVQAS
HiaNm	MNKIYRIIWN	SALNAWVVVS	ELTRNHTKRA	SATVKTAVLA	TLLFATVQAS
h15	MNKIYRIIWN	SALNAWVVVS	ELTRNHTKRA	SATVATAVLA	TLLFATVQAN
BZ10	MNKISRIIWN	SALNAWVVVS	ELTRNHTKRA	SATVATAVLA	TLLFATVQAN
bz198	MNKIYRIIWN	SALNAWVVVS	ELTRNHTKRA	SATVATAVLA	TLLFATVQAN
eg327	MNKIYRIIWN	SALNAWVAVS	ELTRNHTKRA	SATVATAVLA	TLLFATVQAS
h38	MNKIYRIIWN	SALNAWVAVS	ELTRNHTKRA	SATVKTAVLA	TLLFATVQAN
h41	MNKIYRIIWN	SALNAWVAVS	ELTRNHTKRA	SATVKTAVLA	TLLFATVQAN
p20	MNKIYRIIWN	SALNAWVVVS	ELTRNHTKRA	SATVATAVLA	TLLSATVQAN
	51				100
eg329	ANNE.EQEED	LYLDPVLRV	AVLIVNSDKE	GTGEKEKVEE	NSDWAVYFNE
pmc21	ANNE.EQEED	LYLDPVQRTV	AVLIVNSDKE	GTGEKEKVEE	NSDWAVYFNE
HiaNm	ANNERPRKKD	LYLDPVQRTV	AVLIVNSDKE	GTGEKEKVEE	NSDWAVYFNE
h15	ATD....DDD	LYLEPVQRTA	VVLSFRSDKE	GTGEKE.GTE	DSNWAVYFDE
BZ10	ATD....DDD	LYLEPVQRTA	VVLSFRSDKE	GTGEKE.GTE	DSNWAVYFDE
bz198	ATD....DDD	LYLEPVQRTA	VVLSFRSDFE	GTGEKE.GTE	DSNWAVYFDE
eg327	TTD....DDD	LYLEPVQRTA	VVLSFRSDKE	GTGEKE.VTE	DSNWGVYFDK
h38	ATDE...DEE	EELEPVVRS	LVLQFMIDKE	NGENE.STG	NIGWSIYYDN
h41	ATDE...DEE	EELESVQRS	VVGSIQASME	GSVELETI...	..SLSMTNDS
p20	ATDT...DED	EELESVARSA	LVLQFMIDKE	GNGEIE.STG	DIGWSIYYDD
	101				150
eg329	KGVLTA.REI	TLKAGDNLKI	KQ.....	..NGTNFTYS	LKKDLTDLTS
pmc21	KGVLTA.REI	TLKAGDNLKI	KQ.....	..NGTNFTYS	LKKDLTDLTS
HiaNm	KGVLTA.REI	TLKAGDNLKI	KQ.....	..NGTNFTYS	LKKDLTDLTS
h15	KRVLKA.GAI	TLKAGDNLKI	KQNTNENTNE	NTNDSSFTYS	LKKDLTDLTS
BZ10	KRVLKA.GAI	TLKAGDNLKI	KQNTNENTNE	NTNDSSFTYS	LKKDLTDLTS
bz198	KRVLKA.GAI	TLKAGDNLKI	KQ....NTNE	NTNDSSFTYS	LKKDLTDLTS
eg327	KGVLTA.GTI	TLKAGDNLKI	KQ....NTNE	NTNASSFTYS	LKKDLTDLTS
h38	HNTLHG.ATV	TLKAGDNLKI	KQNTNKNENTNE	NTNDSSFTYS	LKKDLTDLTS
h41	KEFVDPYIVV	TLKAGDNLKI	KQ....NTNE	NTNASSFTYS	LKKDLTGLIN
p20	HNTLHG.ATV	TLKAGDNLKI	KQ.....	..SGKDFTYS	LKKELKDLTS
	151				200
eg329	VGTEKLSFSA	NGNKVNITSD	TKGLNFAKET	AGTNGDPTVH	LNGIGSTLTD
pmc21	VGTEKLSFSA	NGNKVNITSD	TKGLNFAKET	AGTNGDPTVH	LNGIGSTLTD
HiaNm	VGTEKLSFSA	NGNKVNITSD	TKGLNFAKET	AGTNGDPTVH	LNGIGSTLTD
h15	VETEKLSTFGA	NGNKVNITSD	TKGLNFAKET	AGTNGDPTVH	LNGIGSTLTD
BZ10	VETEKLSTFGA	NGNKVNITSD	TKGLNFAKET	AGTNGDPTVH	LNGIGSTLTD
bz198	VETEKLSTFGA	NGNKVNITSD	TKGLNFAKET	AGTNGDPTVH	LNGIGSTLTD
eg327	VGTEKLSFSA	NSNKVNITSD	TKGLNFAKKT	AETNGDPTVH	LNGIGSTLTD
h38	VETEKLSTFGA	NGNKVNITSD	TKGLNFAKET	AGTNGDPTVH	LNGIGSTLTD
h41	VETEKLSTFGA	NGKKVNIISD	TKGLNFAKET	AGTNGDPTVH	LNGIGSTLTD
p20	VETEKLSTFGA	NGNKVNITSD	TKGLNFAKET	AGTNGDPTVH	LNGIGSTLTD

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FIG. 7 cont'd

	201				250
eg329	TLLNTGATTN	VTNDNVTDDDE	KKRAASVKDV	LNAGWNIKGV	KPGTTA..SD
pmc21	TLLNTGATTN	VTNDNVTDDDE	KKRAASVKDV	LNAGWNIKGV	KPGTTA..SD
HiaNm	TLLNTGATTN	VTNDNVTDDDE	KKRAASVKDV	LNAGWNIKGV	KPGTTA..SD
h15	TLLNTGATTN	VTNDNVTDDDE	KKRAASVKDV	LNAGWNIKGV	KPGTTA..SD
BZ10	TLLNTGATTN	VTNDNVTDDDE	KKRAASVKDV	LNAGWNIKGV	KPGTTA..SD
bz198	TLLNTGATTN	VTNDNVTDDDE	KKRAASVKDV	LNAGWNIKGV	KPGTTA..SD
eg327	TLLNTGATTN	VTNDNVTDDDE	KKRAASVKDV	LNAGWNIKGV	KPGTTA..SD
h38	TLLNTGATTN	VTNDNVTDDK	KKRAASVKDV	LNAGWNIKGV	KPGTTA..SD
h41	MLLNTGATTN	VTNDNVTDDDE	KKRAASVKDV	LNAGWNIKGV	KPGTTA..SD
p20	TLAGSSASHV	DAGNQSTHY.	.TRAASIKDV	LNAGWNIKGV	KTGSTTGQSE
	251				300
eg329	NVDFVRTYDT	VEFLSADTKT	TTVNVESKDN	GKKTEVKIGA	KTSVIEKEDG
pmc21	NVDFVRTYDT	VEFLSADTKT	TTVNVESKDN	GKKTEVKIGA	KTSVIEKEDG
HiaNm	NVDFVRTYDT	VEFLSADTKT	TTVNVESKDN	GKKTEVKIGV	KTSVIEKEDG
h15	NVDFVRTYDT	VEFLSADTKT	TTVNVESKDN	GKKTEVKIGA	KTSVIEKEDG
BZ10	NVDFVRTYDT	VEFLSADTKT	TTVNVESKDN	GKRTEVKIGA	KTSVIEKEDG
bz198	NVDFVRTYDT	VEFLSADTKT	TTVNVESKDN	GKKTEVKIGA	KTSVIEKEDG
eg327	NVDFVRTYDT	VEFLSADTKT	TTVNVESKDN	GKRTEVKIGA	KTSVIEKEDG
h38	NVDFVHTYDT	VEFLSADTKT	TTVNVESKDN	GKRTEVKIGA	KTSVIEKEDG
h41	NVDFVRTYDT	VEFLSADTKT	TTVNVESKDN	GKKTEVKIGA	KTSVIEKEDG
p20	NVDFVRTYDT	VEFLSADTKT	TTVNVESKDN	GKRTEVKIGA	KTSVIEKEDG
	301				350
eg329	KLVTGKDKGE	NGSSTDEGEG	LVTAKEVIDA	VNKAGWRMKT	TTANGQTGQA
pmc21	KLVTGKDKGE	NGSSTDEGEG	LVTAKEVIDA	VNKAGWRMKT	TTANGQTGQA
HiaNm	KLVTGKDKGE	NGSSTDEGEG	LVTAKEVIDA	VNKAGWRMKT	TTANGQTGQA
h15	KLVTGKGKDE	NGSSTDEGEG	LVTAKEVIDA	VNKAGWRMKT	TTANGQTGQA
BZ10	KLVTGKGKGE	NGSSTDEGEG	LVTAKEVIDA	VNKAGWRMKT	TTANGQTGQA
bz198	KLVTGKGKDE	NGSSTDEGEG	LVTAKEVIDA	VNKAGWRMKT	TTANGQTGQA
eg327	KLVTGKDKGE	NDSSTDKEGEG	LVTAKEVIDA	VNKAGWRMKT	TTANGQTGQA
h38	KLVTGKGKGE	NGSSTDEGEG	LVTAKEVIDA	VNKAGWRMKT	TTANGQTGQA
h41	KLVTGKGKGE	NGSSTDEGEG	LVTAKEVIDA	VNKAGWRMKT	TTANGQTGQA
p20	KLVTGKGKGE	NGSSTDEGEG	LVTAKEVIDA	VNKAGWRMKT	TTANGQTGQA
	351				400
eg329	DKFETVTS GT	NVTFASGKGT	TATVSKDDQG	NITVMYDVNV	GDALNVNQLQ
pmc21	DKFETVTS GT	NVTFASGKGT	TATVSKDDQG	NITVMYDVNV	GDALNVNQLQ
HiaNm	DKFETVTS GT	NVTFASGKGT	TATVSKDDQG	NITVMYDVNV	GDALNVNQLQ
h15	DKFETVTS GT	KVTFASGN GT	TATVSKDDQG	NITVKYDVNV	GDALNVNQLQ
BZ10	DKFETVTS GT	KVTFASGN GT	TATVSKDDQG	NITVKYDVNV	GDALNVNQLQ
bz198	DKFETVTS GT	NVTFASGKGT	TATVSKDDQG	NITVKYDVNV	GDALNVNQLQ
eg327	DKFETVTS GT	NVTFASGKGT	TATVSKDDQG	NITVMYDVNV	GDALNVNQLQ
h38	DKFETVTS GT	NVTFASGKGT	TATVSKDDQG	NITVKYDVNV	GDALNVNQLQ
h41	DKFETVTS GT	KVTFASGN GT	TATVSKDDQG	NITVKYDVNV	GDALNVNQLQ
p20	DKFETVTS GT	KVTFASGN GT	TATVSKDDQG	NITVKYDVNV	GDALNVNQLQ

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FIG. 7 cont'd

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pmc21	NSGWNLDSKA	VAGSSGKVIS	GNVSPSKGKM	DETVNINAGN	NIEITRNGKN
HiaNm	NSGWNLDSKA	VAGSSGKVIS	GNVSPSKGKM	DETVNINAGN	NIEITRNGKN
h15	NSGWNLDSKA	VAGSSGKVIS	GNVSPSKGKM	DETVNINAGN	NIEITRNGKN
BZ10	NSGWNLDSKA	VAGSSGKVIS	GNVSPSKGKM	DETVNINAGN	NIEITRNGKN
bz198	NSGWNLDSKA	VAGSSGKVIS	GNVSPSKGKM	DETVNINAGN	NIEITRNGKN
eg327	NSGWNLDSKA	VAGSSGKVIS	GNVSPSKGKM	DETVNINAGN	NIEITRNGKN
h38	NSGWNLDSKA	VAGSSGKVIS	GNVSPSKGKM	DETVNINAGN	NIEITRNGKN
h41	NSGWNLDSKA	VAGSSGKVIS	GNVSPSKGKM	DETVNINAGN	NIEITRNGKN
p20	NSGWNLDSKA	VAGSSGKVIS	GNVSPSKGKM	DETVNINAGN	NIEITRNGKN
	451				500
eg329	IDIATSMTPQ	FSSVSLGAGA	DAPTLSVDGD	.ALNVGSKKD	NKPVRITNVA
pmc21	IDIATSMTPQ	FSSVSLGAGA	DAPTLSVDGD	.ALNVGSKKD	NKPVRITNVA
HiaNm	IDIATSMTPQ	FSSVSLGAGA	DAPTLSVDGD	.ALNVGSKKD	NKPVRITNVA
h15	IDIATSMTPQ	FSSVSLGAGA	DAPTLSVDDE	GALNVGSKDA	NKPVRITNVA
BZ10	IDIATSMTPQ	FSSVSLGAGA	DAPTLSVDDE	GALNVGSKDA	NKPVRITNVA
bz198	IDIATSMTPQ	FSSVSLGAGA	DAPTLSVDDE	GALNVGSKDT	NKPVRITNVA
eg327	IDIATSMTPQ	FSSVSLGAGA	DAPTLSVDDE	GALNVGSKDA	NKPVRITNVA
h38	IDIATSMTPQ	FSSVSLGAGA	DAPTLSVDDK	GALNVGSKDA	NKPVRITNVA
h41	IDIATSMTPQ	FSSVSLGAGA	DAPTLSVDDE	GALNVGSKDA	NKPVRITNVA
p20	IDIATSMTPQ	FSSVSLGAGA	DAPTLSVDDE	GALNVGSKDA	NKPVRITNVA
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pmc21	PGVKEGDVTN	VAQLKGVAQN	LNNRIDNVDG	NARAGIAQAI	ATAGLVQAYL
HiaNm	PGVKEGDVTN	VAQLKGVAQN	LNNRIDNVDG	NARAGIAQAI	ATAGLVQAYL
h15	PGVKEGDVTN	VAQLKGVAQN	LNNRIDNVDG	NARAGIAQAI	ATAGLAQAYL
BZ10	PGVKEGDVTN	VAQLKGVAQN	LNNRIDNVDG	NARAGIAQAI	ATAGLAQAYL
bz198	PGVKEGDVTN	VAQLKGVAQN	LNNRIDNVDG	NARAGIAQAI	ATAGLVQAYL
eg327	PGVKEGDVTN	VAQLKGVAQN	LNNHIDNVDG	NARAGIAQAI	ATAGLVQAYL
h38	PGVKEGDVTN	VAQLKGVAQN	LNNRIDNVDG	NARAGIAQAI	ATAGLVQAYL
h41	PGVKEGDVTN	VAQLKGVAQN	LNNRIDNVNG	NARAGIAQAI	ATAGLVQAYL
p20	PGVKEGDVTN	VAQLKGVAQN	LNNRIDNVNG	NARAGIAQAI	ATAGLAQAYL
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eg329	PGKSMMMAIGG	GTYRGEAGYA	IGYSSISDGG	NWIIKGTASG	NSRGHFGASA
pmc21	PGKSMMMAIGG	GTYRGEAGYA	IGYSSISDGG	NWIIKGTASG	NSRGHFGASA
HiaNm	PGKSMMMAIGG	GTYRGEAGYA	IGYSSISDGG	NWIIKGTASG	NSRGHFGASA
h15	PGKSMMMAIGG	GTYRGEAGYA	IGYSSISDTG	NWVIKGTASG	NSRGHFGASA
BZ10	PGKSMMMAIGG	GTYRGEAGYA	IGYSSISDTG	NWVIKGTASG	NSRGHFGTSA
bz198	PGKSMMMAIGG	DTYRGEAGYA	IGYSSISDGG	NWIIKGTASG	NSRGHFGASA
eg327	PGKSMMMAIGG	GTYRGEAGYA	IGYSSISDGG	NWIIKGTASG	NSRGHFGASA
h38	PGKSMMMAIGG	GTYRGEAGYA	IGYSSISDGG	NWIIKGTASG	NSRGHFGASA
h41	PGKSMMMAIGG	GTYLGEAGYA	IGYSSISAGG	NWIIKGTASG	NSRGHFGASA
p20	PGKSMMMAIGG	GTYLGEAGYA	IGYSSISDTG	NWVIKGTASG	NSRGHFGTSA

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FIG. 7 cont'd

	601
eg329	SVGYQW*
pmc21	SVGYQW*
HiaNm	SVGYQW*
h15	SVGYQW*
BZ10	SVGYQW*
bz198	SVGYQW*
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h38	SVGYQW*
h41	SVGYQW*
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SEQUENCE LISTING

<110> Peak, Ian R. (U.S. only)
 Jennings, Michael P. (U.S. only)
 Moxom, Edward R. (U.S. only)
 University of Queensland (except U.S.)
 Isis Innovations Limited (except U.S.)

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iii

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iv

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V

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Ile Thr Ser Asp Thr Lys Gly Leu Asn Phe Ala Lys Glu Thr Ala Gly
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acg aac ggc gac ccc acg gtt cat ctg aac ggt atc ggt tcg act ttg     576
Thr Asn Gly Asp Pro Thr Val His Leu Asn Gly Ile Gly Ser Thr Leu
             180            185            190

acc gat acg ctg ctg aat acc gga gcg acc aca aac gta acc aac gac     624
Thr Asp Thr Leu Leu Asn Thr Gly Ala Thr Thr Asn Val Thr Asn Asp
             195            200            205

aac gtt acc gat gac gag aaa aaa cgt gcg gca agc gtt aaa gac gta     672
Asn Val Thr Asp Asp Glu Lys Lys Arg Ala Ala Ser Val Lys Asp Val
             210            215            220

tta aac gca ggc tgg aac att aaa ggc gtt aaa ccc ggt aca aca gct     720

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viii

Leu 225	Asn	Ala	Gly	Trp	Asn 230	Ile	Lys	Gly	Val	Lys 235	Pro	Gly	Thr	Thr	Ala 240	
tcc	gat	aac	gtc	gat	ttc	gtc	cgc	act	tac	gac	aca	gtc	gag	ttc	ttg	768
Ser	Asp	Asn	Val	Asp 245	Phe	Val	Arg	Thr	Tyr 250	Asp	Thr	Val	Glu	Phe	Leu 255	
agc	gca	gat	acg	aaa	aca	acg	act	gtt	aat	gtg	gaa	agc	aaa	gac	aac	816
Ser	Ala	Asp	Thr 260	Lys	Thr	Thr	Thr	Val 265	Asn	Val	Glu	Ser	Lys 270	Asp	Asn	
ggc	aag	aga	acc	gaa	gtt	aaa	atc	ggg	gag	aag	act	tct	gtt	att	aaa	864
Gly	Lys	Arg	Thr 275	Glu	Val	Lys	Ile 280	Gly	Ala	Lys	Thr	Ser 285	Val	Ile	Lys	
gaa	aaa	gac	ggg	aag	ttg	gtt	act	ggg	aaa	ggc	aaa	ggc	gag	aat	ggg	912
Glu	Lys	Asp	Gly 290	Lys	Leu	Val 295	Thr	Gly	Lys	Gly	Lys 300	Gly	Glu	Asn	Gly	
tct	tct	aca	gac	gaa	ggc	gaa	ggc	tta	gtg	act	gca	aaa	gaa	gtg	att	960
Ser	Ser	Thr	Asp	Glu	Gly 310	Glu	Gly	Leu	Val	Thr 315	Ala	Lys	Glu	Val	Ile 320	
gat	gca	gta	aac	aag	gct	ggg	tgg	aga	atg	aaa	aca	aca	acc	gct	aat	1008
Asp	Ala	Val	Asn 325	Lys	Ala	Gly	Trp	Arg	Met 330	Lys	Thr	Thr	Thr	Ala	Asn 335	
ggg	caa	aca	ggg	caa	gct	gac	aag	ttt	gaa	acc	gtt	aca	tca	ggc	aca	1056
Gly	Gln	Thr	Gly 340	Gln	Ala	Asp	Lys	Phe 345	Glu	Thr	Val	Thr	Ser 350	Gly	Thr	
aaa	gta	acc	ttt	gct	agt	ggg	aat	ggg	aca	act	gcg	act	gta	agt	aaa	1104
Lys	Val	Thr 355	Phe	Ala	Ser	Gly	Asn 360	Gly	Thr	Thr	Ala	Thr 365	Val	Ser	Lys	
gat	gat	caa	ggc	aac	atc	act	gtt	aag	tat	gat	gta	aat	gtc	ggc	gat	1152
Asp	Asp	Gln	Gly	Asn	Ile 375	Thr	Val	Lys	Tyr	Asp 380	Val	Asn	Val	Gly	Asp	
gcc	cta	aac	gtc	aat	cag	ctg	caa	aac	agc	ggg	tgg	aat	ttg	gat	tcc	1200
Ala	Leu	Asn	Val	Asn 390	Gln	Leu	Gln	Asn	Ser	Gly 395	Trp	Asn	Leu	Asp	Ser 400	
aaa	gcg	gtt	gca	ggg	tct	tcg	ggc	aaa	gtc	atc	agc	ggc	aat	gtt	tcg	1248
Lys	Ala	Val	Ala 405	Gly	Ser	Ser	Gly	Lys 410	Val	Ile	Ser	Gly	Asn 415	Val	Ser	
ccg	agc	aag	gga	aag	atg	gat	gaa	acc	gtc	aac	att	aat	gcc	ggc	aac	1296
Pro	Ser	Lys	Gly 420	Lys	Met	Asp	Glu	Thr 425	Val	Asn	Ile	Asn 430	Ala	Gly	Asn	
aac	atc	gag	att	acc	cgc	aac	ggc	aaa	aat	atc	gac	atc	gcc	act	tcg	1344
Asn	Ile	Glu	Ile 435	Thr	Arg	Asn	Gly	Lys 440	Asn	Ile	Asp	Ile 445	Ala	Thr	Ser	
atg	acc	ccg	caa	ttt	tcc	agc	gtt	tcg	ctc	ggc	gcg	ggg	gcg	gat	gcg	1392
Met	Thr	Pro	Gln 450	Phe	Ser	Ser	Val 455	Ser	Leu	Gly	Ala 460	Gly	Ala	Asp	Ala	
ccc	act	tta	agc	gtg	gat	gac	gag	ggc	gcg	ttg	aat	gtc	ggc	agc	aag	1440
Pro	Thr	Leu	Ser	Val 470	Asp	Asp	Glu	Gly	Ala 475	Leu	Asn	Val	Gly	Ser	Lys 480	
gat	gcc	aac	aaa	ccc	gtc	cgc	att	acc	aat	gtc	gcc	ccg	ggc	gtt	aaa	1488
Asp	Ala	Asn	Lys	Pro	Val	Arg	Ile	Thr	Asn	Val	Ala	Pro	Gly	Val	Lys	

ix

485										490										495										
gag ggg gat gtt aca aac gtc gca caa ctt aaa ggt gtg gcg caa aac	1536																													
Glu Gly Asp Val Thr Asn Val Ala Gln Leu Lys Gly Val Ala Gln Asn																														
500 505 510																														
ttg aac aac cgc atc gac aat gtg gac ggc aac gcg cgc gcg ggt atc	1584																													
Leu Asn Asn Arg Ile Asp Asn Val Asp Gly Asn Ala Arg Ala Gly Ile																														
515 520 525																														
gcc caa gcg att gca acc gca ggt ttg gct cag gcc tat ttg ccc ggc	1632																													
Ala Gln Ala Ile Ala Thr Ala Gly Leu Ala Gln Ala Tyr Leu Pro Gly																														
530 535 540																														
aag agt atg atg gcg atc ggc ggc ggt act tat cgc ggc gaa gcc ggt	1680																													
Lys Ser Met Met Ala Ile Gly Gly Gly Thr Tyr Arg Gly Glu Ala Gly																														
545 550 555 560																														
tac gcc atc ggc tac tcg agc att tct gac act ggg aat tgg gtt atc	1728																													
Tyr Ala Ile Gly Tyr Ser Ser Ile Ser Asp Thr Gly Asn Trp Val Ile																														
565 570 575																														
aag ggc acg gct tcc ggc aat tcg cgc ggt cat ttc ggt act tcc gca	1776																													
Lys Gly Thr Ala Ser Gly Asn Ser Arg Gly His Phe Gly Thr Ser Ala																														
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Ser Val Gly Tyr Gln Trp																														
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<212> PRT

<213> Neisseria meningitidis

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Thr Val Ala Thr Ala Val Leu Ala Thr Leu Leu Phe Ala Thr Val Gln	
35 40 45	
Ala Asn Ala Thr Asp Asp Asp Asp Leu Tyr Leu Glu Pro Val Gln Arg	
50 55 60	
Thr Ala Val Val Leu Ser Phe Arg Ser Asp Lys Glu Gly Thr Gly Glu	
65 70 75 80	
Lys Glu Gly Thr Glu Asp Ser Asn Trp Ala Val Tyr Phe Asp Glu Lys	
85 90 95	
Arg Val Leu Lys Ala Gly Ala Ile Thr Leu Lys Ala Gly Asp Asn Leu	
100 105 110	
Lys Ile Lys Gln Asn Thr Asn Glu Asn Thr Asn Glu Asn Thr Asn Asp	
115 120 125	
Ser Ser Phe Thr Tyr Ser Leu Lys Lys Asp Leu Thr Asp Leu Thr Ser	
130 135 140	
Val Glu Thr Glu Lys Leu Ser Phe Gly Ala Asn Gly Asn Lys Val Asn	

X

145 150 155 160
 Ile Thr Ser Asp Thr Lys Gly Leu Asn Phe Ala Lys Glu Thr Ala Gly
 165 170 175
 Thr Asn Gly Asp Pro Thr Val His Leu Asn Gly Ile Gly Ser Thr Leu
 180 185 190
 Thr Asp Thr Leu Leu Asn Thr Gly Ala Thr Thr Asn Val Thr Asn Asp
 195 200 205
 Asn Val Thr Asp Asp Glu Lys Lys Arg Ala Ala Ser Val Lys Asp Val
 210 215 220
 Leu Asn Ala Gly Trp Asn Ile Lys Gly Val Lys Pro Gly Thr Thr Ala
 225 230 235 240
 Ser Asp Asn Val Asp Phe Val Arg Thr Tyr Asp Thr Val Glu Phe Leu
 245 250 255
 Ser Ala Asp Thr Lys Thr Thr Thr Val Asn Val Glu Ser Lys Asp Asn
 260 265 270
 Gly Lys Arg Thr Glu Val Lys Ile Gly Ala Lys Thr Ser Val Ile Lys
 275 280 285
 Glu Lys Asp Gly Lys Leu Val Thr Gly Lys Gly Lys Gly Glu Asn Gly
 290 295 300
 Ser Ser Thr Asp Glu Gly Glu Gly Leu Val Thr Ala Lys Glu Val Ile
 305 310 315 320
 Asp Ala Val Asn Lys Ala Gly Trp Arg Met Lys Thr Thr Thr Ala Asn
 325 330 335
 Gly Gln Thr Gly Gln Ala Asp Lys Phe Glu Thr Val Thr Ser Gly Thr
 340 345 350
 Lys Val Thr Phe Ala Ser Gly Asn Gly Thr Thr Ala Thr Val Ser Lys
 355 360 365
 Asp Asp Gln Gly Asn Ile Thr Val Lys Tyr Asp Val Asn Val Gly Asp
 370 375 380
 Ala Leu Asn Val Asn Gln Leu Gln Asn Ser Gly Trp Asn Leu Asp Ser
 385 390 395 400
 Lys Ala Val Ala Gly Ser Ser Gly Lys Val Ile Ser Gly Asn Val Ser
 405 410 415
 Pro Ser Lys Gly Lys Met Asp Glu Thr Val Asn Ile Asn Ala Gly Asn
 420 425 430
 Asn Ile Glu Ile Thr Arg Asn Gly Lys Asn Ile Asp Ile Ala Thr Ser
 435 440 445
 Met Thr Pro Gln Phe Ser Ser Val Ser Leu Gly Ala Gly Ala Asp Ala
 450 455 460
 Pro Thr Leu Ser Val Asp Asp Glu Gly Ala Leu Asn Val Gly Ser Lys
 465 470 475 480
 Asp Ala Asn Lys Pro Val Arg Ile Thr Asn Val Ala Pro Gly Val Lys
 485 490 495

xi

Glu Gly Asp Val Thr Asn Val Ala Gln Leu Lys Gly Val Ala Gln Asn
 500 505 510

Leu Asn Asn Arg Ile Asp Asn Val Asp Gly Asn Ala Arg Ala Gly Ile
 515 520 525

Ala Gln Ala Ile Ala Thr Ala Gly Leu Ala Gln Ala Tyr Leu Pro Gly
 530 535 540

Lys Ser Met Met Ala Ile Gly Gly Gly Thr Tyr Arg Gly Glu Ala Gly
 545 550 555 560

Tyr Ala Ile Gly Tyr Ser Ser Ile Ser Asp Thr Gly Asn Trp Val Ile
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Ser Val Gly Tyr Gln Trp
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gtc gtc gta tcc gag ctc aca cgc aac cac acc aaa cgc gcc tcc gca 96
 Val Val Val Ser Glu Leu Thr Arg Asn His Thr Lys Arg Ala Ser Ala
 20 25 30

acc gtg gcg acc gcc gta ttg gcg aca ctg ttg ttt gca acg gtt cag 144
 Thr Val Ala Thr Ala Val Leu Ala Thr Leu Leu Phe Ala Thr Val Gln
 35 40 45

gcg aat gct acc gat gac gac gat tta tat tta gaa ccc gta caa cgc 192
 Ala Asn Ala Thr Asp Asp Asp Asp Leu Tyr Leu Glu Pro Val Gln Arg
 50 55 60

act gct gtc gtg ttg agc ttc cgt tcc gat aaa gaa ggc acg gga gaa 240
 Thr Ala Val Val Leu Ser Phe Arg Ser Asp Lys Glu Gly Thr Gly Glu
 65 70 75 80

aaa gaa ggt aca gaa gat tca aat tgg gca gta tat ttc gac gag aaa 288
 Lys Glu Gly Thr Glu Asp Ser Asn Trp Ala Val Tyr Phe Asp Glu Lys
 85 90 95

aga gta cta aaa gcc gga gca atc acc ctc aaa gcc ggc gac aac ctg 336
 Arg Val Leu Lys Ala Gly Ala Ile Thr Leu Lys Ala Gly Asp Asn Leu
 100 105 110

aaa atc aaa caa aac acc aat gaa aac acc aat gac agt agc ttc acc 384
 Lys Ile Lys Gln Asn Thr Asn Glu Asn Thr Asn Asp Ser Ser Phe Thr
 115 120 125

tac tcc ctg aaa aaa gac ctc aca gat ctg acc agt gtt gaa act gaa 432

xii

Tyr	Ser	Leu	Lys	Lys	Asp	Leu	Thr	Asp	Leu	Thr	Ser	Val	Glu	Thr	Glu	
130						135					140					
aaa	tta	tcg	ttt	ggc	gca	aac	ggg	aat	aaa	gtc	aac	atc	aca	agc	gac	480
Lys	Leu	Ser	Phe	Gly	Ala	Asn	Gly	Asn	Lys	Val	Asn	Ile	Thr	Ser	Asp	
145				150					155						160	
acc	aaa	ggc	ttg	aat	ttt	gcg	aaa	gaa	acg	gct	ggg	acg	aac	ggc	gac	528
Thr	Lys	Gly	Leu	Asn	Phe	Ala	Lys	Glu	Thr	Ala	Gly	Thr	Asn	Gly	Asp	
			165						170					175		
ccc	acg	gtt	cat	ctg	aac	ggg	atc	ggg	tcg	act	ttg	acc	gat	acg	ctg	576
Pro	Thr	Val	His	Leu	Asn	Gly	Ile	Gly	Ser	Thr	Leu	Thr	Asp	Thr	Leu	
			180					185					190			
ctg	aat	acc	gga	gcg	acc	aca	aac	gta	acc	aac	gac	aac	gtt	acc	gat	624
Leu	Asn	Thr	Gly	Ala	Thr	Thr	Asn	Val	Thr	Asn	Asp	Asn	Val	Thr	Asp	
		195					200					205				
gac	gag	aaa	aaa	cgt	gcg	gca	agc	gtt	aaa	gac	gta	tta	aac	gca	ggc	672
Asp	Glu	Lys	Lys	Arg	Ala	Ala	Ser	Val	Lys	Asp	Val	Leu	Asn	Ala	Gly	
	210					215					220					
tgg	aac	att	aaa	ggc	gtt	aaa	ccc	ggg	aca	aca	gct	tcc	gat	aac	gtt	720
Trp	Asn	Ile	Lys	Gly	Val	Lys	Pro	Gly	Thr	Thr	Ala	Ser	Asp	Asn	Val	
	225				230					235					240	
gat	ttc	gtc	cgc	act	tac	gac	aca	gtc	gag	ttc	ttg	agc	gca	gat	acg	768
Asp	Phe	Val	Arg	Thr	Tyr	Asp	Thr	Val	Glu	Phe	Leu	Ser	Ala	Asp	Thr	
			245						250					255		
aaa	aca	acg	act	gtt	aat	gtg	gaa	agc	aaa	gac	aac	ggc	aag	aaa	acc	816
Lys	Thr	Thr	Val	Asn	Val	Glu	Ser	Lys	Asp	Asn	Gly	Lys	Lys	Thr		
			260				265					270				
gaa	gtt	aaa	atc	ggg	gcg	aag	act	tct	gtt	att	aaa	gaa	aaa	gac	ggg	864
Glu	Val	Lys	Ile	Gly	Ala	Lys	Thr	Ser	Val	Ile	Lys	Glu	Lys	Asp	Gly	
		275					280					285				
aag	ttg	gtt	act	ggg	aaa	ggc	aaa	gac	gag	aat	ggg	tct	tct	aca	gac	912
Lys	Leu	Val	Thr	Gly	Lys	Gly	Lys	Asp	Glu	Asn	Gly	Ser	Ser	Thr	Asp	
	290					295					300					
gaa	ggc	gaa	ggc	tta	gtg	act	gca	aaa	gaa	gtg	att	gat	gca	gta	aac	960
Glu	Gly	Glu	Gly	Leu	Val	Thr	Ala	Lys	Glu	Val	Ile	Asp	Ala	Val	Asn	
	305				310					315					320	
aag	gct	ggg	tgg	aga	atg	aaa	aca	aca	acc	gct	aat	ggg	caa	aca	ggg	1008
Lys	Ala	Gly	Trp	Arg	Met	Lys	Thr	Thr	Thr	Ala	Asn	Gly	Gln	Thr	Gly	
			325						330					335		
caa	gct	gac	aag	ttt	gaa	acc	gtt	aca	tca	ggc	aca	aat	gta	acc	ttt	1056
Gln	Ala	Asp	Lys	Phe	Glu	Thr	Val	Thr	Ser	Gly	Thr	Asn	Val	Thr	Phe	
			340					345					350			
gct	agt	ggg	aaa	ggg	aca	act	gcg	act	gta	agt	aaa	gat	gat	caa	ggc	1104
Ala	Ser	Gly	Lys	Gly	Thr	Thr	Ala	Thr	Val	Ser	Lys	Asp	Asp	Gln	Gly	
		355					360					365				
aac	atc	act	gtt	aag	tat	gat	gta	aat	gtc	ggc	gat	gcc	cta	aac	gtc	1152
Asn	Ile	Thr	Val	Lys	Tyr	Asp	Val	Asn	Val	Gly	Asp	Ala	Leu	Asn	Val	
	370					375					380					
aat	cag	ctg	caa	aac	agc	ggg	tgg	aat	ttg	gat	tcc	aaa	gcg	gtt	gca	1200
Asn	Gln	Leu	Gln	Asn	Ser	Gly	Trp	Asn	Leu	Asp	Ser	Lys	Ala	Val	Ala	

xiii

385	390	395	400	
ggt tct tcg ggc aaa gtc atc agc ggc aat gtt tcg ccg agc aag gga				1248
Gly Ser Ser Gly Lys Val Ile Ser Gly Asn Val Ser Pro Ser Lys Gly	405	410	415	
aag atg gat gaa acc gtc aac att aat gcc ggc aac aac atc gag att				1296
Lys Met Asp Glu Thr Val Asn Ile Asn Ala Gly Asn Asn Ile Glu Ile	420	425	430	
acc cgc aac ggt aaa aat atc gac atc gcc act tcg atg gcg ccg cag				1344
Thr Arg Asn Gly Lys Asn Ile Asp Ile Ala Thr Ser Met Ala Pro Gln	435	440	445	
ttt tcc agc gtt tcg ctc ggt gcg ggg gcg gat gcg ccc act ttg agc				1392
Phe Ser Ser Val Ser Leu Gly Ala Gly Ala Asp Ala Pro Thr Leu Ser	450	455	460	
gtg gat gac gag ggc gcg ttg aat gtc ggc agc aag gat acc aac aaa				1440
Val Asp Asp Glu Gly Ala Leu Asn Val Gly Ser Lys Asp Thr Asn Lys	465	470	475	480
ccc gtc cgc att acc aat gtc gcc ccg ggc gtt aaa gag ggg gat gtt				1488
Pro Val Arg Ile Thr Asn Val Ala Pro Gly Val Lys Glu Gly Asp Val	485	490	495	
aca aac gtc gca caa ctt aaa ggc gtg gcg caa aac ttg aac aac cgc				1536
Thr Asn Val Ala Gln Leu Lys Gly Val Ala Gln Asn Leu Asn Asn Arg	500	505	510	
atc gac aat gtg gac ggc aac gcg cgt gcg ggc atc gcc caa gcg att				1584
Ile Asp Asn Val Asp Gly Asn Ala Arg Ala Gly Ile Ala Gln Ala Ile	515	520	525	
gca acc gca ggt cta gtt cag gcg tat ctg ccc ggc aag agt atg atg				1632
Ala Thr Ala Gly Leu Val Gln Ala Tyr Leu Pro Gly Lys Ser Met Met	530	535	540	
gcg atc ggc ggc gac act tat cgc ggc gaa gcc ggt tac gcc atc ggc				1680
Ala Ile Gly Gly Asp Thr Tyr Arg Gly Glu Ala Gly Tyr Ala Ile Gly	545	550	555	560
tac tca agt att tcc gac ggc gga aat tgg att atc aaa ggc acg gct				1728
Tyr Ser Ser Ile Ser Asp Gly Gly Asn Trp Ile Ile Lys Gly Thr Ala	565	570	575	
tcc ggc aat tcg cgc ggc cat ttc ggt gct tcc gca tct gtc ggt tat				1776
Ser Gly Asn Ser Arg Gly His Phe Gly Ala Ser Ala Ser Val Gly Tyr	580	585	590	
caa tgg taa				1785
Gln Trp	595			

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 <212> PRT
 <213> Neisseria meningitidis

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xiv

20										25										30										
Thr	Val	Ala	Thr	Ala	Val	Leu	Ala	Thr	Leu	Leu	Phe	Ala	Thr	Val	Gln															
		35					40					45																		
Ala	Asn	Ala	Thr	Asp	Asp	Asp	Asp	Leu	Tyr	Leu	Glu	Pro	Val	Gln	Arg															
	50					55					60																			
Thr	Ala	Val	Val	Leu	Ser	Phe	Arg	Ser	Asp	Lys	Glu	Gly	Thr	Gly	Glu															
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Lys	Glu	Gly	Thr	Glu	Asp	Ser	Asn	Trp	Ala	Val	Tyr	Phe	Asp	Glu	Lys															
				85				90						95																
Arg	Val	Leu	Lys	Ala	Gly	Ala	Ile	Thr	Leu	Lys	Ala	Gly	Asp	Asn	Leu															
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Lys	Ile	Lys	Gln	Asn	Thr	Asn	Glu	Asn	Thr	Asn	Asp	Ser	Ser	Phe	Thr															
	115					120						125																		
Tyr	Ser	Leu	Lys	Lys	Asp	Leu	Thr	Asp	Leu	Thr	Ser	Val	Glu	Thr	Glu															
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Thr	Lys	Gly	Leu	Asn	Phe	Ala	Lys	Glu	Thr	Ala	Gly	Thr	Asn	Gly	Asp															
			165					170						175																
Pro	Thr	Val	His	Leu	Asn	Gly	Ile	Gly	Ser	Thr	Leu	Thr	Asp	Thr	Leu															
		180					185						190																	
Leu	Asn	Thr	Gly	Ala	Thr	Thr	Asn	Val	Thr	Asn	Asp	Asn	Val	Thr	Asp															
	195						200					205																		
Asp	Glu	Lys	Lys	Arg	Ala	Ala	Ser	Val	Lys	Asp	Val	Leu	Asn	Ala	Gly															
	210					215					220																			
Trp	Asn	Ile	Lys	Gly	Val	Lys	Pro	Gly	Thr	Thr	Ala	Ser	Asp	Asn	Val															
	225				230					235					240															
Asp	Phe	Val	Arg	Thr	Tyr	Asp	Thr	Val	Glu	Phe	Leu	Ser	Ala	Asp	Thr															
			245						250					255																
Lys	Thr	Thr	Thr	Val	Asn	Val	Glu	Ser	Lys	Asp	Asn	Gly	Lys	Lys	Thr															
		260					265						270																	
Glu	Val	Lys	Ile	Gly	Ala	Lys	Thr	Ser	Val	Ile	Lys	Glu	Lys	Asp	Gly															
	275					280						285																		
Lys	Leu	Val	Thr	Gly	Lys	Gly	Lys	Asp	Glu	Asn	Gly	Ser	Ser	Thr	Asp															
	290					295					300																			
Glu	Gly	Glu	Gly	Leu	Val	Thr	Ala	Lys	Glu	Val	Ile	Asp	Ala	Val	Asn															
	305				310					315					320															
Lys	Ala	Gly	Trp	Arg	Met	Lys	Thr	Thr	Thr	Ala	Asn	Gly	Gln	Thr	Gly															
			325						330					335																
Gln	Ala	Asp	Lys	Phe	Glu	Thr	Val	Thr	Ser	Gly	Thr	Asn	Val	Thr	Phe															
		340					345						350																	
Ala	Ser	Gly	Lys	Gly	Thr	Thr	Ala	Thr	Val	Ser	Lys	Asp	Asp	Gln	Gly															
		355					360					365																		

XV

Asn Ile Thr Val Lys Tyr Asp Val Asn Val Gly Asp Ala Leu Asn Val
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 Asn Gln Leu Gln Asn Ser Gly Trp Asn Leu Asp Ser Lys Ala Val Ala
 385 390 395 400
 Gly Ser Ser Gly Lys Val Ile Ser Gly Asn Val Ser Pro Ser Lys Gly
 405 410 415
 Lys Met Asp Glu Thr Val Asn Ile Asn Ala Gly Asn Asn Ile Glu Ile
 420 425 430
 Thr Arg Asn Gly Lys Asn Ile Asp Ile Ala Thr Ser Met Ala Pro Gln
 435 440 445
 Phe Ser Ser Val Ser Leu Gly Ala Gly Ala Asp Ala Pro Thr Leu Ser
 450 455 460
 Val Asp Asp Glu Gly Ala Leu Asn Val Gly Ser Lys Asp Thr Asn Lys
 465 470 475 480
 Pro Val Arg Ile Thr Asn Val Ala Pro Gly Val Lys Glu Gly Asp Val
 485 490 495
 Thr Asn Val Ala Gln Leu Lys Gly Val Ala Gln Asn Leu Asn Asn Arg
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 Ile Asp Asn Val Asp Gly Asn Ala Arg Ala Gly Ile Ala Gln Ala Ile
 515 520 525
 Ala Thr Ala Gly Leu Val Gln Ala Tyr Leu Pro Gly Lys Ser Met Met
 530 535 540
 Ala Ile Gly Gly Asp Thr Tyr Arg Gly Glu Ala Gly Tyr Ala Ile Gly
 545 550 555 560
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Gln Trp

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 <221> CDS
 <222> (1)..(1785)

<400> 8
 atg aac aaa ata tac cgc atc att tgg aat agt gcc ctc aat gcc tgg 48
 Met Asn Lys Ile Tyr Arg Ile Ile Trp Asn Ser Ala Leu Asn Ala Trp
 1 5 10 15
 gtc gcc gta tcc gag ctc aca cgc aac cac acc aaa cgc gcc tcc gca 96
 Val Ala Val Ser Glu Leu Thr Arg Asn His Thr Lys Arg Ala Ser Ala
 20 25 30
 acc gtg gcg acc gcc gta ttg gcg aca ctg ttg ttt gca acg gtt cag 144
 Thr Val Ala Thr Ala Val Leu Ala Thr Leu Leu Phe Ala Thr Val Gln

xvi

35	40	45	
gcg agt act acc gat gac gac gat tta tat tta gaa ccc gta caa cgc			192
Ala Ser Thr Thr Asp Asp Asp Asp Leu Tyr Leu Glu Pro Val Gln Arg			
50	55	60	
act gct gtc gtg ttg agc ttc cgt tcc gat aaa gaa ggc acg gga gaa			240
Thr Ala Val Val Leu Ser Phe Arg Ser Asp Lys Glu Gly Thr Gly Glu			
65	70	75	80
aaa gaa gtt aca gaa gat tca aat tgg gga gta tat ttc gac aag aaa			288
Lys Glu Val Thr Glu Asp Ser Asn Trp Gly Val Tyr Phe Asp Lys Lys			
85	90	95	
gga gta cta aca gcc gga aca atc acc ctc aaa gcc ggc gac aac ctg			336
Gly Val Leu Thr Ala Gly Thr Ile Thr Leu Lys Ala Gly Asp Asn Leu			
100	105	110	
aaa atc aaa caa aac acc aat gaa aac acc aat gcc agt agc ttc acc			384
Lys Ile Lys Gln Asn Thr Asn Glu Asn Thr Asn Ala Ser Ser Phe Thr			
115	120	125	
tac tcg ctg aaa aaa gac ctc aca gat ctg acc agt gtt gga act gaa			432
Tyr Ser Leu Lys Lys Asp Leu Thr Asp Leu Thr Ser Val Gly Thr Glu			
130	135	140	
aaa tta tcg ttt agc gca aac agc aat aaa gtc aac atc aca agc gac			480
Lys Leu Ser Phe Ser Ala Asn Ser Asn Lys Val Asn Ile Thr Ser Asp			
145	150	155	160
acc aaa ggc ttg aat ttc gcg aaa aaa acg gct gag acc aac ggc gac			528
Thr Lys Gly Leu Asn Phe Ala Lys Lys Thr Ala Glu Thr Asn Gly Asp			
165	170	175	
acc acg gtt cat ctg aac ggt atc ggt tcg act ttg acc gat acg ctg			576
Thr Thr Val His Leu Asn Gly Ile Gly Ser Thr Leu Thr Asp Thr Leu			
180	185	190	
ctg aat acc gga gcg acc aca aac gta acc aac gac aac gtt acc gat			624
Leu Asn Thr Gly Ala Thr Thr Asn Val Thr Asn Asp Asn Val Thr Asp			
195	200	205	
gac gag aaa aaa cgt gcg gca agc gtt aaa gac gta tta aac gca ggc			672
Asp Glu Lys Lys Arg Ala Ala Ser Val Lys Asp Val Leu Asn Ala Gly			
210	215	220	
tgg aac att aaa ggc gtt aaa ccc ggt aca aca gct tcc gat aac gtt			720
Trp Asn Ile Lys Gly Val Lys Pro Gly Thr Thr Ala Ser Asp Asn Val			
225	230	235	240
gat ttc gtc cgc act tac gac aca gtc gag ttc ttg agc gca gat acg			768
Asp Phe Val Arg Thr Tyr Asp Thr Val Glu Phe Leu Ser Ala Asp Thr			
245	250	255	
aaa aca acg act gtt aat gtg gaa agc aaa gac aac ggc aag aga acc			816
Lys Thr Thr Val Asn Val Glu Ser Lys Asp Asn Gly Lys Arg Thr			
260	265	270	
gaa gtt aaa atc ggt gcg aag act tct gtt atc aaa gaa aaa gac ggt			864
Glu Val Lys Ile Gly Ala Lys Thr Ser Val Ile Lys Glu Lys Asp Gly			
275	280	285	
aag ttg gtt act ggt aaa gac aaa ggc gag aat gat tct tct aca gac			912
Lys Leu Val Thr Gly Lys Asp Lys Gly Glu Asn Asp Ser Ser Thr Asp			
290	295	300	

Substitute Sheet
(Rule 26) RO/AU

xvii

aaa Lys 305	ggc Gly	gaa Glu	ggc Gly	tta Leu	gtg Val 310	act Thr	gca Ala	aaa Lys	gaa Glu	gtg Val 315	att Ile	gat Asp	gca Ala	gta Val	aac Asn 320	960
aag Lys	gct Ala	ggg Gly	tgg Trp	aga Arg 325	atg Met	aaa Lys	aca Thr	aca Thr	acc Thr 330	gct Ala	aat Asn	ggg Gly	caa Gln	aca Thr 335	ggg Gly	1008
caa Gln	gct Ala	gac Asp	aag Lys 340	ttt Phe	gaa Glu	acc Thr	gtt Val 345	aca Thr	tca Ser	ggc Gly	aca Thr	aat Asn	gta Val 350	acc Thr	ttt Phe	1056
gct Ala	agt Ser	ggg Gly 355	aaa Lys	ggg Gly	aca Thr	act Thr	gcg Ala 360	act Thr	gta Val	agt Ser	aaa Lys	gat Asp 365	gat Asp	caa Gln	ggc Gly	1104
aac Asn 370	atc Ile	act Thr	gtt Val	atg Met	tat Tyr	gat Asp 375	gta Val	aat Asn	gtc Val	ggc Gly	gat Asp 380	gcc Ala	cta Leu	aac Asn	gtc Val	1152
aat Asn 385	cag Gln	ctg Leu	caa Gln	aac Asn	agc Ser 390	ggg Gly	tgg Trp	aat Asn	ttg Leu	gat Asp 395	tcc Ser	aaa Lys	gcg Ala	gtt Val	gca Ala 400	1200
ggg Gly	tct Ser	tcg Ser	ggc Gly	aaa Lys 405	gtc Val	atc Ile	agc Ser	ggc Gly	aat Asn 410	gtt Val	tcg Ser	ccg Pro	agc Ser	aag Lys 415	gga Gly	1248
aag Lys	atg Met	gat Asp	gaa Glu 420	acc Thr	gtc Val	aac Asn	att Ile	aat Asn 425	gcc Ala	ggc Gly	aac Asn	aac Asn	atc Ile 430	gag Glu	att Ile	1296
acc Thr	cgc Arg	aac Asn 435	ggc Gly	aaa Lys	aat Asn	atc Ile	gac Asp 440	atc Ile	gcc Ala	act Thr	tcg Ser	atg Met 445	acc Thr	ccg Pro	caa Gln	1344
ttt Phe 450	tcc Ser	agc Ser	gtt Val	tcg Ser	ctc Leu	ggc Gly 455	gcg Ala	ggg Gly	gcg Ala	gat Asp	gcg Ala	ccc Pro	act Thr	tta Leu	agc Ser	1392
gtg Val 465	gat Asp	gac Asp	gag Glu	ggc Gly	gcg Ala 470	ttg Leu	aat Asn	gtc Val	ggc Gly	agc Ser 475	aag Lys	gat Asp	gcc Ala	aac Asn	aaa Lys 480	1440
ccc Pro	gtc Val	cgc Arg	att Ile	acc Thr 485	aat Asn	gtc Val	gcc Ala	ccg Pro	ggc Gly 490	gtt Val	aaa Lys	gag Glu	ggg Gly	gat Asp 495	gtt Val	1488
aca Thr	aac Asn	gtc Val	gca Ala 500	caa Gln	ctt Leu	aaa Lys	ggc Gly	gtg Val 505	gcg Ala	caa Gln	aac Asn	ttg Leu	aac Asn 510	aac Asn	cac His	1536
atc Ile	gac Asp	aat Asn 515	gtg Val	gac Asp	ggc Gly	aac Asn	gcg Ala 520	cgt Arg	gcg Ala	ggc Gly	atc Ile	gcc Ala 525	caa Gln	gcg Ala	att Ile	1584
gca Ala	acc Thr 530	gca Ala	ggg Gly	ctg Leu	gtt Val	cag Gln 535	gcg Ala	tat Tyr	ctg Leu	ccc Pro	ggc Gly 540	aag Lys	agt Ser	atg Met	atg Met	1632
gcg Ala 545	atc Ile	ggc Gly	ggc Gly	ggc Gly	act Thr 550	tat Tyr	cgc Arg	ggc Gly	gaa Glu	gcc Ala 555	ggg Gly	tat Tyr	gcc Ala	atc Ile	ggc Gly 560	1680

xviii

tac tca agc att tcc gac ggc gga aat tgg att atc aaa ggc acg gct 1728
 Tyr Ser Ser Ile Ser Asp Gly Gly Asn Trp Ile Ile Lys Gly Thr Ala
 565 570 575

tcc ggc aat tcg cgc ggc cat ttc ggt gct tcc gca tct gtc ggt tat 1776
 Ser Gly Asn Ser Arg Gly His Phe Gly Ala Ser Ala Ser Val Gly Tyr
 580 585 590

cag tgg taa 1785
 Gln Trp
 595

<210> 9

<211> 594

<212> PRT

<213> Neisseria meningitidis

<400> 9

Met Asn Lys Ile Tyr Arg Ile Ile Trp Asn Ser Ala Leu Asn Ala Trp
 1 5 10 15

Val Ala Val Ser Glu Leu Thr Arg Asn His Thr Lys Arg Ala Ser Ala
 20 25 30

Thr Val Ala Thr Ala Val Leu Ala Thr Leu Leu Phe Ala Thr Val Gln
 35 40 45

Ala Ser Thr Thr Asp Asp Asp Asp Leu Tyr Leu Glu Pro Val Gln Arg
 50 55 60

Thr Ala Val Val Leu Ser Phe Arg Ser Asp Lys Glu Gly Thr Gly Glu
 65 70 75 80

Lys Glu Val Thr Glu Asp Ser Asn Trp Gly Val Tyr Phe Asp Lys Lys
 85 90 95

Gly Val Leu Thr Ala Gly Thr Ile Thr Leu Lys Ala Gly Asp Asn Leu
 100 105 110

Lys Ile Lys Gln Asn Thr Asn Glu Asn Thr Asn Ala Ser Ser Phe Thr
 115 120 125

Tyr Ser Leu Lys Lys Asp Leu Thr Asp Leu Thr Ser Val Gly Thr Glu
 130 135 140

Lys Leu Ser Phe Ser Ala Asn Ser Asn Lys Val Asn Ile Thr Ser Asp
 145 150 155 160

Thr Lys Gly Leu Asn Phe Ala Lys Lys Thr Ala Glu Thr Asn Gly Asp
 165 170 175

Thr Thr Val His Leu Asn Gly Ile Gly Ser Thr Leu Thr Asp Thr Leu
 180 185 190

Leu Asn Thr Gly Ala Thr Thr Asn Val Thr Asn Asp Asn Val Thr Asp
 195 200 205

Asp Glu Lys Lys Arg Ala Ala Ser Val Lys Asp Val Leu Asn Ala Gly
 210 215 220

Trp Asn Ile Lys Gly Val Lys Pro Gly Thr Thr Ala Ser Asp Asn Val
 225 230 235 240

Asp Phe Val Arg Thr Tyr Asp Thr Val Glu Phe Leu Ser Ala Asp Thr

xix

245										250				255			
Lys	Thr	Thr	Thr	Val	Asn	Val	Glu	Ser	Lys	Asp	Asn	Gly	Lys	Arg	Thr		
			260					265					270				
Glu	Val	Lys	Ile	Gly	Ala	Lys	Thr	Ser	Val	Ile	Lys	Glu	Lys	Asp	Gly		
		275					280					285					
Lys	Leu	Val	Thr	Gly	Lys	Asp	Lys	Gly	Glu	Asn	Asp	Ser	Ser	Thr	Asp		
	290					295					300						
Lys	Gly	Glu	Gly	Leu	Val	Thr	Ala	Lys	Glu	Val	Ile	Asp	Ala	Val	Asn		
	305				310						315				320		
Lys	Ala	Gly	Trp	Arg	Met	Lys	Thr	Thr	Thr	Ala	Asn	Gly	Gln	Thr	Gly		
				325					330					335			
Gln	Ala	Asp	Lys	Phe	Glu	Thr	Val	Thr	Ser	Gly	Thr	Asn	Val	Thr	Phe		
			340					345					350				
Ala	Ser	Gly	Lys	Gly	Thr	Thr	Ala	Thr	Val	Ser	Lys	Asp	Asp	Gln	Gly		
		355					360					365					
Asn	Ile	Thr	Val	Met	Tyr	Asp	Val	Asn	Val	Gly	Asp	Ala	Leu	Asn	Val		
	370					375					380						
Asn	Gln	Leu	Gln	Asn	Ser	Gly	Trp	Asn	Leu	Asp	Ser	Lys	Ala	Val	Ala		
	385				390						395				400		
Gly	Ser	Ser	Gly	Lys	Val	Ile	Ser	Gly	Asn	Val	Ser	Pro	Ser	Lys	Gly		
				405					410					415			
Lys	Met	Asp	Glu	Thr	Val	Asn	Ile	Asn	Ala	Gly	Asn	Asn	Ile	Glu	Ile		
			420					425					430				
Thr	Arg	Asn	Gly	Lys	Asn	Ile	Asp	Ile	Ala	Thr	Ser	Met	Thr	Pro	Gln		
		435					440					445					
Phe	Ser	Ser	Val	Ser	Leu	Gly	Ala	Gly	Ala	Asp	Ala	Pro	Thr	Leu	Ser		
	450					455					460						
Val	Asp	Asp	Glu	Gly	Ala	Leu	Asn	Val	Gly	Ser	Lys	Asp	Ala	Asn	Lys		
	465				470						475				480		
Pro	Val	Arg	Ile	Thr	Asn	Val	Ala	Pro	Gly	Val	Lys	Glu	Gly	Asp	Val		
				485					490					495			
Thr	Asn	Val	Ala	Gln	Leu	Lys	Gly	Val	Ala	Gln	Asn	Leu	Asn	Asn	His		
			500					505					510				
Ile	Asp	Asn	Val	Asp	Gly	Asn	Ala	Arg	Ala	Gly	Ile	Ala	Gln	Ala	Ile		
		515					520					525					
Ala	Thr	Ala	Gly	Leu	Val	Gln	Ala	Tyr	Leu	Pro	Gly	Lys	Ser	Met	Met		
		530				535					540						
Ala	Ile	Gly	Gly	Gly	Thr	Tyr	Arg	Gly	Glu	Ala	Gly	Tyr	Ala	Ile	Gly		
	545				550						555				560		
Tyr	Ser	Ser	Ile	Ser	Asp	Gly	Gly	Asn	Trp	Ile	Ile	Lys	Gly	Thr	Ala		
				565					570					575			
Ser	Gly	Asn	Ser	Arg	Gly	His	Phe	Gly	Ala	Ser	Ala	Ser	Val	Gly	Tyr		

XX

Gln Trp

<210> 10
 <211> 1776
 <212> DNA
 <213> Neisseria meningitidis

<220>
 <221> CDS
 <222> (1)..(1776)

<400> 10
 atg aac gaa ata ttg cgc atc att tgg aat agc gcc ctc aat gcc tgg 48
 Met Asn Glu Ile Leu Arg Ile Ile Trp Asn Ser Ala Leu Asn Ala Trp
 1 5 10 15

gtc gtt gta tcc gag ctc aca cgc aac cac acc aaa cgc gcc tcc gca 96
 Val Val Val Ser Glu Leu Thr Arg Asn His Thr Lys Arg Ala Ser Ala
 20 25 30

acc gtg aag acc gcc gta ttg gcg act ctg ttg ttt gca acg gtt cag 144
 Thr Val Lys Thr Ala Val Leu Ala Thr Leu Leu Phe Ala Thr Val Gln
 35 40 45

gca agt gct aac aat gaa gag caa gaa gaa gat tta tat tta gac ccc 192
 Ala Ser Ala Asn Asn Glu Glu Gln Glu Glu Asp Leu Tyr Leu Asp Pro
 50 55 60

gtg cta cgc act gtt gcc gtg ttg ata gtc aat tcc gat aaa gaa ggc 240
 Val Leu Arg Thr Val Ala Val Leu Ile Val Asn Ser Asp Lys Glu Gly
 65 70 75 80

acg gga gaa aaa gaa aaa gta gaa gaa aat tca gat tgg gca gta tat 288
 Thr Gly Glu Lys Glu Lys Val Glu Glu Asn Ser Asp Trp Ala Val Tyr
 85 90 95

ttc aac gag aaa gga gta cta aca gcc aga gaa atc acc ctc aaa gcc 336
 Phe Asn Glu Lys Gly Val Leu Thr Ala Arg Glu Ile Thr Leu Lys Ala
 100 105 110

ggc gac aac ctg aaa atc aaa caa aac ggc aca aac ttc acc tac tcg 384
 Gly Asp Asn Leu Lys Ile Lys Gln Asn Gly Thr Asn Phe Thr Tyr Ser
 115 120 125

ctg aaa aaa gac ctc aca gat ctg acc agt gtt gga act gaa aaa tta 432
 Leu Lys Lys Asp Leu Thr Asp Leu Thr Ser Val Gly Thr Glu Lys Leu
 130 135 140

tcg ttt agc gca aac ggc aat aaa gtc aac atc aca agc gac acc aaa 480
 Ser Phe Ser Ala Asn Gly Asn Lys Val Asn Ile Thr Ser Asp Thr Lys
 145 150 155 160

ggc ttg aat ttt gcg aaa gaa acg gct ggg acg aac ggc gac acc acg 528
 Gly Leu Asn Phe Ala Lys Glu Thr Ala Gly Thr Asn Gly Asp Thr Thr
 165 170 175

gtt cat ctg aac ggt att ggt tcg act ttg acc gat acg ctg ctg aat 576
 Val His Leu Asn Gly Ile Gly Ser Thr Leu Thr Asp Thr Leu Leu Asn
 180 185 190

acc gga gcg acc aca aac gta acc aac gac aac gtt acc gat gac gag 624
 Thr Gly Ala Thr Thr Asn Val Thr Asn Asp Asn Val Thr Asp Asp Glu
 195 200 205

xxi

aaa aaa cgt gcg gca agc gtt aaa gac gta tta aac gct ggc tgg aac 672
 Lys Lys Arg Ala Ala Ser Val Lys Asp Val Leu Asn Ala Gly Trp Asn
 210 215 220

att aaa ggc gtt aaa ccc ggt aca aca gct tcc gat aac gtt gat ttc 720
 Ile Lys Gly Val Lys Pro Gly Thr Thr Ala Ser Asp Asn Val Asp Phe
 225 230 235 240

gtc cgc act tac gac aca gtc gag ttc ttg agc gca gat acg aaa aca 768
 Val Arg Thr Tyr Asp Thr Val Glu Phe Leu Ser Ala Asp Thr Lys Thr
 245 250 255

acg act gtt aat gtg gaa agc aaa gac aac ggc aag aaa acc gaa gtt 816
 Thr Thr Val Asn Val Glu Ser Lys Asp Asn Gly Lys Lys Thr Glu Val
 260 265 270

aaa atc ggt gcg aag act tct gtt att aaa gaa aaa gac ggt aag ttg 864
 Lys Ile Gly Ala Lys Thr Ser Val Ile Lys Glu Lys Asp Gly Lys Leu
 275 280 285

gtt act ggt aaa gac aaa ggc gag aat ggt tct tct aca gac gaa ggc 912
 Val Thr Gly Lys Asp Lys Gly Glu Asn Gly Ser Ser Thr Asp Glu Gly
 290 295 300

gaa ggc tta gtg act gca aaa gaa gtg att gat gca gta aac aag gct 960
 Glu Gly Leu Val Thr Ala Lys Glu Val Ile Asp Ala Val Asn Lys Ala
 305 310 315 320

ggt tgg aga atg aaa aca aca acc gct aat ggt caa aca ggt caa gct 1008
 Gly Trp Arg Met Lys Thr Thr Thr Ala Asn Gly Gln Thr Gly Gln Ala
 325 330 335

gac aag ttt gaa acc gtt aca tca ggc aca aat gta acc ttt gct agt 1056
 Asp Lys Phe Glu Thr Val Thr Ser Gly Thr Asn Val Thr Phe Ala Ser
 340 345 350

ggt aaa ggt aca act gcg act gta agt aaa gat gat caa ggc aac atc 1104
 Gly Lys Gly Thr Thr Ala Thr Val Ser Lys Asp Asp Gln Gly Asn Ile
 355 360 365

act gtt atg tat gat gta aat gtc ggc gat gcc cta aac gtc aat cag 1152
 Thr Val Met Tyr Asp Val Asn Val Gly Asp Ala Leu Asn Val Asn Gln
 370 375 380

ctg caa aac agc ggt tgg aat ttg gat tcc aaa gcg gtt gca ggt tct 1200
 Leu Gln Asn Ser Gly Trp Asn Leu Asp Ser Lys Ala Val Ala Gly Ser
 385 390 395 400

tcg ggc aaa gtc atc agc ggc aat gtt tcg ccg agc aag gga aag atg 1248
 Ser Gly Lys Val Ile Ser Gly Asn Val Ser Pro Ser Lys Gly Lys Met
 405 410 415

gat gaa acc gtc aac att aat gcc ggc aac aac atc gag att acc cgc 1296
 Asp Glu Thr Val Asn Ile Asn Ala Gly Asn Asn Ile Glu Ile Thr Arg
 420 425 430

aac ggt aaa aat atc gac atc gcc act tcg atg acc ccg cag ttt tcc 1344
 Asn Gly Lys Asn Ile Asp Ile Ala Thr Ser Met Thr Pro Gln Phe Ser
 435 440 445

agc gtt tcg ctc ggc gcg ggg gcg gat gcg ccc act ttg agc gtg gat 1392
 Ser Val Ser Leu Gly Ala Gly Ala Asp Ala Pro Thr Leu Ser Val Asp
 450 455 460

ggg gac gca ttg aat gtc ggc agc aag aag gac aac aaa ccc gtc cgc 1440

xxii

Gly Asp Ala Leu Asn Val Gly Ser Lys Lys Asp Asn Lys Pro Val Arg
 465 470 475 480

att acc aat gtc gcc ccg ggc gtt aaa gag ggg gat gtt aca aac gtc 1488
 Ile Thr Asn Val Ala Pro Gly Val Lys Glu Gly Asp Val Thr Asn Val
 485 490 495

gca caa ctt aaa ggc gtg gcg caa aac ttg aac aac cgc atc gac aat 1536
 Ala Gln Leu Lys Gly Val Ala Gln Asn Leu Asn Asn Arg Ile Asp Asn
 500 505 510

gtg gac ggc aac gcg cgt gcg ggc atc gcc caa gcg att gca acc gca 1584
 Val Asp Gly Asn Ala Arg Ala Gly Ile Ala Gln Ala Ile Ala Thr Ala
 515 520 525

ggc ctg gtt cag gcg tat ttg ccc ggc aag agt atg atg gcg atc ggc 1632
 Gly Leu Val Gln Ala Tyr Leu Pro Gly Lys Ser Met Met Ala Ile Gly
 530 535 540

ggc ggc act tat cgc ggc gaa gcc ggt tac gcc atc ggc tac tcc agt 1680
 Gly Gly Thr Tyr Arg Gly Glu Ala Gly Tyr Ala Ile Gly Tyr Ser Ser
 545 550 555 560

att tcc gac ggc gga aat tgg att atc aaa ggc acg gct tcc ggc aat 1728
 Ile Ser Asp Gly Gly Asn Trp Ile Ile Lys Gly Thr Ala Ser Gly Asn
 565 570 575

tcg cgc ggc cat ttc ggt gct tcc gca tct gtc ggt tat cag tgg taa 1776
 Ser Arg Gly His Phe Gly Ala Ser Ala Ser Val Gly Tyr Gln Trp
 580 585 590

<210> 11
 <211> 591
 <212> PRT
 <213> Neisseria meningitidis

<400> 11
 Met Asn Glu Ile Leu Arg Ile Ile Trp Asn Ser Ala Leu Asn Ala Trp
 1 5 10 15

Val Val Val Ser Glu Leu Thr Arg Asn His Thr Lys Arg Ala Ser Ala
 20 25 30

Thr Val Lys Thr Ala Val Leu Ala Thr Leu Leu Phe Ala Thr Val Gln
 35 40 45

Ala Ser Ala Asn Asn Glu Glu Gln Glu Glu Asp Leu Tyr Leu Asp Pro
 50 55 60

Val Leu Arg Thr Val Ala Val Leu Ile Val Asn Ser Asp Lys Glu Gly
 65 70 75 80

Thr Gly Glu Lys Glu Lys Val Glu Glu Asn Ser Asp Trp Ala Val Tyr
 85 90 95

Phe Asn Glu Lys Gly Val Leu Thr Ala Arg Glu Ile Thr Leu Lys Ala
 100 105 110

Gly Asp Asn Leu Lys Ile Lys Gln Asn Gly Thr Asn Phe Thr Tyr Ser
 115 120 125

Leu Lys Lys Asp Leu Thr Asp Leu Thr Ser Val Gly Thr Glu Lys Leu
 130 135 140

xxiii

Ser Phe Ser Ala Asn Gly Asn Lys Val Asn Ile Thr Ser Asp Thr Lys
 145 150 155 160
 Gly Leu Asn Phe Ala Lys Glu Thr Ala Gly Thr Asn Gly Asp Thr Thr
 165 170 175
 Val His Leu Asn Gly Ile Gly Ser Thr Leu Thr Asp Thr Leu Leu Asn
 180 185 190
 Thr Gly Ala Thr Thr Asn Val Thr Asn Asp Asn Val Thr Asp Asp Glu
 195 200 205
 Lys Lys Arg Ala Ala Ser Val Lys Asp Val Leu Asn Ala Gly Trp Asn
 210 215 220
 Ile Lys Gly Val Lys Pro Gly Thr Thr Ala Ser Asp Asn Val Asp Phe
 225 230 235 240
 Val Arg Thr Tyr Asp Thr Val Glu Phe Leu Ser Ala Asp Thr Lys Thr
 245 250 255
 Thr Thr Val Asn Val Glu Ser Lys Asp Asn Gly Lys Lys Thr Glu Val
 260 265 270
 Lys Ile Gly Ala Lys Thr Ser Val Ile Lys Glu Lys Asp Gly Lys Leu
 275 280 285
 Val Thr Gly Lys Asp Lys Gly Glu Asn Gly Ser Ser Thr Asp Glu Gly
 290 295 300
 Glu Gly Leu Val Thr Ala Lys Glu Val Ile Asp Ala Val Asn Lys Ala
 305 310 315 320
 Gly Trp Arg Met Lys Thr Thr Thr Ala Asn Gly Gln Thr Gly Gln Ala
 325 330 335
 Asp Lys Phe Glu Thr Val Thr Ser Gly Thr Asn Val Thr Phe Ala Ser
 340 345 350
 Gly Lys Gly Thr Thr Ala Thr Val Ser Lys Asp Asp Gln Gly Asn Ile
 355 360 365
 Thr Val Met Tyr Asp Val Asn Val Gly Asp Ala Leu Asn Val Asn Gln
 370 375 380
 Leu Gln Asn Ser Gly Trp Asn Leu Asp Ser Lys Ala Val Ala Gly Ser
 385 390 395 400
 Ser Gly Lys Val Ile Ser Gly Asn Val Ser Pro Ser Lys Gly Lys Met
 405 410 415
 Asp Glu Thr Val Asn Ile Asn Ala Gly Asn Asn Ile Glu Ile Thr Arg
 420 425 430
 Asn Gly Lys Asn Ile Asp Ile Ala Thr Ser Met Thr Pro Gln Phe Ser
 435 440 445
 Ser Val Ser Leu Gly Ala Gly Ala Asp Ala Pro Thr Leu Ser Val Asp
 450 455 460
 Gly Asp Ala Leu Asn Val Gly Ser Lys Lys Asp Asn Lys Pro Val Arg
 465 470 475 480
 Ile Thr Asn Val Ala Pro Gly Val Lys Glu Gly Asp Val Thr Asn Val
 485 490 495

xxiv

Ala Gln Leu Lys Gly Val Ala Gln Asn Leu Asn Asn Arg Ile Asp Asn
500 505 510

Val Asp Gly Asn Ala Arg Ala Gly Ile Ala Gln Ala Ile Ala Thr Ala
515 520 525

Gly Leu Val Gln Ala Tyr Leu Pro Gly Lys Ser Met Met Ala Ile Gly
530 535 540

Gly Gly Thr Tyr Arg Gly Glu Ala Gly Tyr Ala Ile Gly Tyr Ser Ser
545 550 555 560

Ile Ser Asp Gly Gly Asn Trp Ile Ile Lys Gly Thr Ala Ser Gly Asn
565 570 575

Ser Arg Gly His Phe Gly Ala Ser Ala Ser Val Gly Tyr Gln Trp
580 585 590

<210> 12
<211> 1797
<212> DNA
<213> Neisseria meningitidis

<220>
<221> CDS
<222> (1)..(1797)

<400> 12
atg aac aaa ata tac cgc atc att tgg aat agt gcc ctc aat gcc tgg 48
Met Asn Lys Ile Tyr Arg Ile Ile Trp Asn Ser Ala Leu Asn Ala Trp
1 5 10 15

gtc gtc gta tcc gag ctc aca cgc aac cac acc aaa cgc gcc tcc gca 96
Val Val Val Ser Glu Leu Thr Arg Asn His Thr Lys Arg Ala Ser Ala
20 25 30

acc gtg gcg acc gcc gta ttg gcg aca ctg ttg ttt gca acg gtt cag 144
Thr Val Ala Thr Ala Val Leu Ala Thr Leu Leu Phe Ala Thr Val Gln
35 40 45

gcg aat gct acc gat gac gac gat tta tat tta gaa ccc gta caa cgc 192
Ala Asn Ala Thr Asp Asp Asp Asp Leu Tyr Leu Glu Pro Val Gln Arg
50 55 60

act gct gtc gtg ttg agc ttc cgt tcc gat aaa gaa ggc acg gga gaa 240
Thr Ala Val Val Leu Ser Phe Arg Ser Asp Lys Glu Gly Thr Gly Glu
65 70 75 80

aaa gaa ggt aca gaa gat tca aat tgg gca gta tat ttc gac gag aaa 288
Lys Glu Gly Thr Glu Asp Ser Asn Trp Ala Val Tyr Phe Asp Glu Lys
85 90 95

aga gta cta aaa gcc gga gca atc acc ctc aaa gcc ggc gac aac ctg 336
Arg Val Leu Lys Ala Gly Ala Ile Thr Leu Lys Ala Gly Asp Asn Leu
100 105 110

aaa atc aaa caa aac acc aat gaa aac acc aat gaa aac acc aat gac 384
Lys Ile Lys Gln Asn Thr Asn Glu Asn Thr Asn Glu Asn Thr Asn Asp
115 120 125

agt agc ttc acc tac tcc ctg aaa aaa gac ctc aca gat ctg acc agt 432
Ser Ser Phe Thr Tyr Ser Leu Lys Lys Asp Leu Thr Asp Leu Thr Ser
130 135 140

XXV

gtt gaa act gaa aaa tta tcg ttt ggc gca aac ggt aat aaa gtc aac 480
 Val Glu Thr Glu Lys Leu Ser Phe Gly Ala Asn Gly Asn Lys Val Asn
 145 150 155 160

atc aca agc gac acc aaa ggc ttg aat ttt gcg aaa gaa acg gct ggg 528
 Ile Thr Ser Asp Thr Lys Gly Leu Asn Phe Ala Lys Glu Thr Ala Gly
 165 170 175

acg aac ggc gac ccc acg gtt cat ctg aac ggt atc ggt tcg act ttg 576
 Thr Asn Gly Asp Pro Thr Val His Leu Asn Gly Ile Gly Ser Thr Leu
 180 185 190

acc gat acg ctg ctg aat acc gga gcg acc aca aac gta acc aac gac 624
 Thr Asp Thr Leu Leu Asn Thr Gly Ala Thr Thr Asn Val Thr Asn Asp
 195 200 205

aac gtt acc gat gac gag aaa aaa cgt gcg gca agc gtt aaa gac gta 672
 Asn Val Thr Asp Asp Glu Lys Lys Arg Ala Ala Ser Val Lys Asp Val
 210 215 220

tta aac gca ggc tgg aac att aaa ggc gtt aaa ccc ggt aca aca gct 720
 Leu Asn Ala Gly Trp Asn Ile Lys Gly Val Lys Pro Gly Thr Thr Ala
 225 230 235 240

tcc gat aac gtt gat ttc gtc cgc act tac gac aca gtc gag ttc ttg 768
 Ser Asp Asn Val Asp Phe Val Arg Thr Tyr Asp Thr Val Glu Phe Leu
 245 250 255

agc gca gat acg aaa aca acg act gtt aat gtg gaa agc aaa gac aac 816
 Ser Ala Asp Thr Lys Thr Thr Thr Val Asn Val Glu Ser Lys Asp Asn
 260 265 270

ggc aag aaa acc gaa gtt aaa atc ggt gcg aag act tct gtt att aaa 864
 Gly Lys Lys Thr Glu Val Lys Ile Gly Ala Lys Thr Ser Val Ile Lys
 275 280 285

gaa aaa gac ggt aag ttg gtt act ggt aaa ggc aaa gac gag aat ggt 912
 Glu Lys Asp Gly Lys Leu Val Thr Gly Lys Gly Lys Asp Glu Asn Gly
 290 295 300

tct tct aca gac gaa ggc gaa ggc tta gtg act gca aaa gaa gtg att 960
 Ser Ser Thr Asp Glu Gly Glu Gly Leu Val Thr Ala Lys Glu Val Ile
 305 310 315 320

gat gca gta aac aag gct ggt tgg aga atg aaa aca aca acc gct aat 1008
 Asp Ala Val Asn Lys Ala Gly Trp Arg Met Lys Thr Thr Thr Ala Asn
 325 330 335

ggt caa aca ggt caa gct gac aag ttt gaa acc gtt aca tca ggc aca 1056
 Gly Gln Thr Gly Gln Ala Asp Lys Phe Glu Thr Val Thr Ser Gly Thr
 340 345 350

aaa gta acc ttt gct agt ggt aat ggt aca act gcg act gta agt aaa 1104
 Lys Val Thr Phe Ala Ser Gly Asn Gly Thr Thr Ala Thr Val Ser Lys
 355 360 365

gat gat caa ggc aac atc act gtt aag tat gat gta aat gtc ggc gat 1152
 Asp Asp Gln Gly Asn Ile Thr Val Lys Tyr Asp Val Asn Val Gly Asp
 370 375 380

gcc cta aac gtc aat cag ctg caa aac agc ggt tgg aat ttg gat tcc 1200
 Ala Leu Asn Val Asn Gln Leu Gln Asn Ser Gly Trp Asn Leu Asp Ser
 385 390 395 400

xxvi

aaa gcg gtt gca ggt tct tcg ggc aaa gtc atc agc ggc aat gtt tcg 1248
 Lys Ala Val Ala Gly Ser Ser Gly Lys Val Ile Ser Gly Asn Val Ser
 405 410 415

ccg agc aag gga aag atg gat gaa acc gtc aac att aat gcc ggc aac 1296
 Pro Ser Lys Gly Lys Met Asp Glu Thr Val Asn Ile Asn Ala Gly Asn
 420 425 430

aac atc gag att acc cgc aac ggc aaa aat atc gac atc gcc act tcg 1344
 Asn Ile Glu Ile Thr Arg Asn Gly Lys Asn Ile Asp Ile Ala Thr Ser
 435 440 445

atg acc ccg caa ttt tcc agc gtt tcg ctc ggc gcg ggg gcg gat gcg 1392
 Met Thr Pro Gln Phe Ser Ser Val Ser Leu Gly Ala Gly Ala Asp Ala
 450 455 460

ccc act tta agc gtg gat gac gag ggc gcg ttg aat gtc ggc agc aag 1440
 Pro Thr Leu Ser Val Asp Asp Glu Gly Ala Leu Asn Val Gly Ser Lys
 465 470 475 480

gat gcc aac aaa ccc gtc cgc att acc aat gtc gcc ccg ggc gtt aaa 1488
 Asp Ala Asn Lys Pro Val Arg Ile Thr Asn Val Ala Pro Gly Val Lys
 485 490 495

gag ggg gat gtt aca aac gtc gca caa ctt aaa ggt gtg gcg caa aac 1536
 Glu Gly Asp Val Thr Asn Val Ala Gln Leu Lys Gly Val Ala Gln Asn
 500 505 510

ttg aac aac cgc atc gac aat gtg gac ggc aac gcg cgc gcg ggt atc 1584
 Leu Asn Asn Arg Ile Asp Asn Val Asp Gly Asn Ala Arg Ala Gly Ile
 515 520 525

gcc caa gcg att gca acc gca ggt ttg gct cag gcg tat ttg ccc ggc 1632
 Ala Gln Ala Ile Ala Thr Ala Gly Leu Ala Gln Ala Tyr Leu Pro Gly
 530 535 540

aag agt atg atg gcg atc ggc ggc ggt act tat cgc ggc gaa gcc ggt 1680
 Lys Ser Met Met Ala Ile Gly Gly Gly Thr Tyr Arg Gly Glu Ala Gly
 545 550 555 560

tac gcc atc ggc tac tcg agc att tct gac act ggg aat tgg gtt atc 1728
 Tyr Ala Ile Gly Tyr Ser Ser Ile Ser Asp Thr Gly Asn Trp Val Ile
 565 570 575

aag ggc acg gct tcc ggc aat tcg cgc ggc cat ttc ggt gct tcc gca 1776
 Lys Gly Thr Ala Ser Gly Asn Ser Arg Gly His Phe Gly Ala Ser Ala
 580 585 590

tct gtc ggt tat cag tgg taa 1797
 Ser Val Gly Tyr Gln Trp
 595

<210> 13
 <211> 598
 <212> PRT
 <213> Neisseria meningitidis

<400> 13
 Met Asn Lys Ile Tyr Arg Ile Ile Trp Asn Ser Ala Leu Asn Ala Trp
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 Val Val Val Ser Glu Leu Thr Arg Asn His Thr Lys Arg Ala Ser Ala
 20 25 30

xxvii

Thr Val Ala Thr Ala Val Leu Ala Thr Leu Leu Phe Ala Thr Val Gln
 35 40 45
 Ala Asn Ala Thr Asp Asp Asp Asp Leu Tyr Leu Glu Pro Val Gln Arg
 50 55 60
 Thr Ala Val Val Leu Ser Phe Arg Ser Asp Lys Glu Gly Thr Gly Glu
 65 70 75 80
 Lys Glu Gly Thr Glu Asp Ser Asn Trp Ala Val Tyr Phe Asp Glu Lys
 85 90 95
 Arg Val Leu Lys Ala Gly Ala Ile Thr Leu Lys Ala Gly Asp Asn Leu
 100 105 110
 Lys Ile Lys Gln Asn Thr Asn Glu Asn Thr Asn Glu Asn Thr Asn Asp
 115 120 125
 Ser Ser Phe Thr Tyr Ser Leu Lys Lys Asp Leu Thr Asp Leu Thr Ser
 130 135 140
 Val Glu Thr Glu Lys Leu Ser Phe Gly Ala Asn Gly Asn Lys Val Asn
 145 150 155 160
 Ile Thr Ser Asp Thr Lys Gly Leu Asn Phe Ala Lys Glu Thr Ala Gly
 165 170 175
 Thr Asn Gly Asp Pro Thr Val His Leu Asn Gly Ile Gly Ser Thr Leu
 180 185 190
 Thr Asp Thr Leu Leu Asn Thr Gly Ala Thr Thr Asn Val Thr Asn Asp
 195 200 205
 Asn Val Thr Asp Asp Glu Lys Lys Arg Ala Ala Ser Val Lys Asp Val
 210 215 220
 Leu Asn Ala Gly Trp Asn Ile Lys Gly Val Lys Pro Gly Thr Thr Ala
 225 230 235 240
 Ser Asp Asn Val Asp Phe Val Arg Thr Tyr Asp Thr Val Glu Phe Leu
 245 250 255
 Ser Ala Asp Thr Lys Thr Thr Thr Val Asn Val Glu Ser Lys Asp Asn
 260 265 270
 Gly Lys Lys Thr Glu Val Lys Ile Gly Ala Lys Thr Ser Val Ile Lys
 275 280 285
 Glu Lys Asp Gly Lys Leu Val Thr Gly Lys Gly Lys Asp Glu Asn Gly
 290 295 300
 Ser Ser Thr Asp Glu Gly Glu Gly Leu Val Thr Ala Lys Glu Val Ile
 305 310 315 320
 Asp Ala Val Asn Lys Ala Gly Trp Arg Met Lys Thr Thr Thr Ala Asn
 325 330 335
 Gly Gln Thr Gly Gln Ala Asp Lys Phe Glu Thr Val Thr Ser Gly Thr
 340 345 350
 Lys Val Thr Phe Ala Ser Gly Asn Gly Thr Thr Ala Thr Val Ser Lys
 355 360 365
 Asp Asp Gln Gly Asn Ile Thr Val Lys Tyr Asp Val Asn Val Gly Asp
 370 375 380

xxviii

Ala Leu Asn Val Asn Gln Leu Gln Asn Ser Gly Trp Asn Leu Asp Ser
385 390 395 400

Lys Ala Val Ala Gly Ser Ser Gly Lys Val Ile Ser Gly Asn Val Ser
405 410 415

Pro Ser Lys Gly Lys Met Asp Glu Thr Val Asn Ile Asn Ala Gly Asn
420 425 430

Asn Ile Glu Ile Thr Arg Asn Gly Lys Asn Ile Asp Ile Ala Thr Ser
435 440 445

Met Thr Pro Gln Phe Ser Ser Val Ser Leu Gly Ala Gly Ala Asp Ala
450 455 460

Pro Thr Leu Ser Val Asp Asp Glu Gly Ala Leu Asn Val Gly Ser Lys
465 470 475 480

Asp Ala Asn Lys Pro Val Arg Ile Thr Asn Val Ala Pro Gly Val Lys
485 490 495

Glu Gly Asp Val Thr Asn Val Ala Gln Leu Lys Gly Val Ala Gln Asn
500 505 510

Leu Asn Asn Arg Ile Asp Asn Val Asp Gly Asn Ala Arg Ala Gly Ile
515 520 525

Ala Gln Ala Ile Ala Thr Ala Gly Leu Ala Gln Ala Tyr Leu Pro Gly
530 535 540

Lys Ser Met Met Ala Ile Gly Gly Gly Thr Tyr Arg Gly Glu Ala Gly
545 550 555 560

Tyr Ala Ile Gly Tyr Ser Ser Ile Ser Asp Thr Gly Asn Trp Val Ile
565 570 575

Lys Gly Thr Ala Ser Gly Asn Ser Arg Gly His Phe Gly Ala Ser Ala
580 585 590

Ser Val Gly Tyr Gln Trp
595

<210> 14
<211> 1800
<212> DNA
<213> Neisseria meningitidis

<220>
<221> CDS
<222> (1)..(1800)

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Met Asn Lys Ile Tyr Arg Ile Ile Trp Asn Ser Ala Leu Asn Ala Trp
1 5 10 15

gtc gcc gta tcc gag ctc aca cgc aac cac acc aaa cgc gcc tcc gca 96
Val Ala Val Ser Glu Leu Thr Arg Asn His Thr Lys Arg Ala Ser Ala
20 25 30

acc gtg aag acc gcc gta ttg gcg acg ctg ttg ttt gca acg gtt cag 144
Thr Val Lys Thr Ala Val Leu Ala Thr Leu Leu Phe Ala Thr Val Gln
35 40 45

xxix

gcg aat gct acc gat gaa gat gaa gaa gaa gag tta gaa ccc gta gta 192
 Ala Asn Ala Thr Asp Glu Asp Glu Glu Glu Glu Leu Glu Pro Val Val
 50 55 60

cgc tct gct ctg gtg ttg caa ttc atg atc gat aaa gaa ggc aat gga 240
 Arg Ser Ala Leu Val Leu Gln Phe Met Ile Asp Lys Glu Gly Asn Gly
 65 70 75 80

gaa aac gaa tct aca gga aat ata ggt tgg agt ata tat tac gac aat 288
 Glu Asn Glu Ser Thr Gly Asn Ile Gly Trp Ser Ile Tyr Tyr Asp Asn
 85 90 95

cac aac act cta cac ggc gca acc gtt acc ctc aaa gcc ggc gac aac 336
 His Asn Thr Leu His Gly Ala Thr Val Thr Leu Lys Ala Gly Asp Asn
 100 105 110

ctg aaa atc aaa caa aac acc aat aaa aac acc aat gaa aac acc aat 384
 Leu Lys Ile Lys Gln Asn Thr Asn Lys Asn Thr Asn Glu Asn Thr Asn
 115 120 125

gac agt agc ttc acc tac tcg ctg aaa aaa gac ctc aca gat ctg acc 432
 Asp Ser Ser Phe Thr Tyr Ser Leu Lys Lys Asp Leu Thr Asp Leu Thr
 130 135 140

agt gtt gaa act gaa aaa tta tcg ttt ggc gca aac ggc aat aaa gtc 480
 Ser Val Glu Thr Glu Lys Leu Ser Phe Gly Ala Asn Gly Asn Lys Val
 145 150 155 160

aac atc aca agc gac acc aaa ggc ttg aat ttc gcg aaa gaa acg gct 528
 Asn Ile Thr Ser Asp Thr Lys Gly Leu Asn Phe Ala Lys Glu Thr Ala
 165 170 175

ggg acg aac ggc gac acc acg gtt cat ctg aac ggt att ggt tcg act 576
 Gly Thr Asn Gly Asp Thr Thr Val His Leu Asn Gly Ile Gly Ser Thr
 180 185 190

ttg acc gat acg ctg ctg aat acc gga gcg acc aca aac gta acc aac 624
 Leu Thr Asp Thr Leu Leu Asn Thr Gly Ala Thr Thr Asn Val Thr Asn
 195 200 205

gac aac gtt acc gat gac aag aaa aaa cgt gcg gca agc gtt aaa gac 672
 Asp Asn Val Thr Asp Asp Lys Lys Lys Arg Ala Ala Ser Val Lys Asp
 210 215 220

gta tta aac gca ggc tgg aac att aaa ggc gtt aaa ccc ggt aca aca 720
 Val Leu Asn Ala Gly Trp Asn Ile Lys Gly Val Lys Pro Gly Thr Thr
 225 230 235 240

gct tcc gat aac gtt gat ttc gtc cac act tac gac aca gtc gag ttc 768
 Ala Ser Asp Asn Val Asp Phe Val His Thr Tyr Asp Thr Val Glu Phe
 245 250 255

ttg agc gca gat acg aaa aca acg act gtt aat gtg gaa agc aaa gac 816
 Leu Ser Ala Asp Thr Lys Thr Thr Thr Val Asn Val Glu Ser Lys Asp
 260 265 270

aac ggc aag aga acc gaa gtt aaa atc ggt gcg aag act tct gtt att 864
 Asn Gly Lys Arg Thr Glu Val Lys Ile Gly Ala Lys Thr Ser Val Ile
 275 280 285

aaa gaa aaa gac ggt aag ttg gtt act ggt aaa ggc aaa ggc gag aat 912
 Lys Glu Lys Asp Gly Lys Leu Val Thr Gly Lys Gly Lys Gly Glu Asn
 290 295 300

XXX

ggt tct tct aca gac gaa ggc gaa ggc tta gtg act gca aaa gaa gtg 960
 Gly Ser Ser Thr Asp Glu Gly Glu Gly Leu Val Thr Ala Lys Glu Val
 305 310 315 320

att gat gca gta aac aag gct ggt tgg aga atg aaa aca aca acc gct 1008
 Ile Asp Ala Val Asn Lys Ala Gly Trp Arg Met Lys Thr Thr Ala
 325 330 335

aat ggt caa aca ggt caa gct gac aag ttt gaa acc gtt aca tca ggc 1056
 Asn Gly Gln Thr Gly Gln Ala Asp Lys Phe Glu Thr Val Thr Ser Gly
 340 345 350

aca aat gta acc ttt gct agt ggt aaa ggt aca act gcg act gta agt 1104
 Thr Asn Val Thr Phe Ala Ser Gly Lys Gly Thr Thr Ala Thr Val Ser
 355 360 365

aaa gat gat caa ggc aac atc act gtt aag tat gat gta aat gtc ggc 1152
 Lys Asp Asp Gln Gly Asn Ile Thr Val Lys Tyr Asp Val Asn Val Gly
 370 375 380

gat gcc cta aac gtc aat cag ctg caa aac agc ggt tgg aat ttg gat 1200
 Asp Ala Leu Asn Val Asn Gln Leu Gln Asn Ser Gly Trp Asn Leu Asp
 385 390 395 400

tcc aaa gcg gtt gca ggt tct tcg ggc aaa gtc atc agc ggc aat gtt 1248
 Ser Lys Ala Val Ala Gly Ser Ser Gly Lys Val Ile Ser Gly Asn Val
 405 410 415

tcg ccg agc aag gga aag atg gat gaa acc gtc aac att aat gcc ggc 1296
 Ser Pro Ser Lys Gly Lys Met Asp Glu Thr Val Asn Ile Asn Ala Gly
 420 425 430

aac aac atc gag att acc cgc aac ggt aaa aat atc gac atc gcc act 1344
 Asn Asn Ile Glu Ile Thr Arg Asn Gly Lys Asn Ile Asp Ile Ala Thr
 435 440 445

tcg atg acc ccg cag ttt tcc agc gtt tcg ctc ggc gcg ggg gcg gat 1392
 Ser Met Thr Pro Gln Phe Ser Ser Val Ser Leu Gly Ala Gly Ala Asp
 450 455 460

gcg ccc act ttg agc gtg gat gac aag ggc gcg ttg aat gtc ggc agc 1440
 Ala Pro Thr Leu Ser Val Asp Asp Lys Gly Ala Leu Asn Val Gly Ser
 465 470 475 480

aag gat gcc aac aaa ccc gtc cgc att acc aat gtc gcc ccg ggc gtt 1488
 Lys Asp Ala Asn Lys Pro Val Arg Ile Thr Asn Val Ala Pro Gly Val
 485 490 495

aaa gag ggg gat gtt aca aac gtc gca caa ctt aaa ggc gtg gcg caa 1536
 Lys Glu Gly Asp Val Thr Asn Val Ala Gln Leu Lys Gly Val Ala Gln
 500 505 510

aac ttg aac aac cgc atc gac aat gtg gac ggc aac gcg cgt gcg ggc 1584
 Asn Leu Asn Asn Arg Ile Asp Asn Val Asp Gly Asn Ala Arg Ala Gly
 515 520 525

atc gcc caa gcg att gca acc gca ggt ctg gtt cag gcg tat ctg ccc 1632
 Ile Ala Gln Ala Ile Ala Thr Ala Gly Leu Val Gln Ala Tyr Leu Pro
 530 535 540

ggc aag agt atg atg gcg atc ggc ggc ggc act tat cgc ggc gaa gcc 1680
 Gly Lys Ser Met Met Ala Ile Gly Gly Gly Thr Tyr Arg Gly Glu Ala
 545 550 555 560

ggt tac gcc atc ggc tac tcc agt att tcc gac ggc gga aat tgg att 1728

xxxii

Leu Ser Ala Asp Thr Lys Thr Thr Thr Val Asn Val Glu Ser Lys Asp
 260 265 270
 Asn Gly Lys Arg Thr Glu Val Lys Ile Gly Ala Lys Thr Ser Val Ile
 275 280 285
 Lys Glu Lys Asp Gly Lys Leu Val Thr Gly Lys Gly Lys Gly Glu Asn
 290 295 300
 Gly Ser Ser Thr Asp Glu Gly Glu Gly Leu Val Thr Ala Lys Glu Val
 305 310 315 320
 Ile Asp Ala Val Asn Lys Ala Gly Trp Arg Met Lys Thr Thr Thr Ala
 325 330 335
 Asn Gly Gln Thr Gly Gln Ala Asp Lys Phe Glu Thr Val Thr Ser Gly
 340 345 350
 Thr Asn Val Thr Phe Ala Ser Gly Lys Gly Thr Thr Ala Thr Val Ser
 355 360 365
 Lys Asp Asp Gln Gly Asn Ile Thr Val Lys Tyr Asp Val Asn Val Gly
 370 375 380
 Asp Ala Leu Asn Val Asn Gln Leu Gln Asn Ser Gly Trp Asn Leu Asp
 385 390 395 400
 Ser Lys Ala Val Ala Gly Ser Ser Gly Lys Val Ile Ser Gly Asn Val
 405 410 415
 Ser Pro Ser Lys Gly Lys Met Asp Glu Thr Val Asn Ile Asn Ala Gly
 420 425 430
 Asn Asn Ile Glu Ile Thr Arg Asn Gly Lys Asn Ile Asp Ile Ala Thr
 435 440 445
 Ser Met Thr Pro Gln Phe Ser Ser Val Ser Leu Gly Ala Gly Ala Asp
 450 455 460
 Ala Pro Thr Leu Ser Val Asp Asp Lys Gly Ala Leu Asn Val Gly Ser
 465 470 475 480
 Lys Asp Ala Asn Lys Pro Val Arg Ile Thr Asn Val Ala Pro Gly Val
 485 490 495
 Lys Glu Gly Asp Val Thr Asn Val Ala Gln Leu Lys Gly Val Ala Gln
 500 505 510
 Asn Leu Asn Asn Arg Ile Asp Asn Val Asp Gly Asn Ala Arg Ala Gly
 515 520 525
 Ile Ala Gln Ala Ile Ala Thr Ala Gly Leu Val Gln Ala Tyr Leu Pro
 530 535 540
 Gly Lys Ser Met Met Ala Ile Gly Gly Gly Thr Tyr Arg Gly Glu Ala
 545 550 555 560
 Gly Tyr Ala Ile Gly Tyr Ser Ser Ile Ser Asp Gly Gly Asn Trp Ile
 565 570 575
 Ile Lys Gly Thr Ala Ser Gly Asn Ser Arg Gly His Phe Gly Ala Ser
 580 585 590
 Ala Ser Val Gly Tyr Gln Trp

xxxiii

595

<210> 16
 <211> 1779
 <212> DNA
 <213> Neisseria meningitidis

<220>
 <221> CDS
 <222> (1)..(1779)

<400> 16
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 Met Asn Lys Ile Tyr Arg Ile Ile Trp Asn Ser Ala Leu Asn Ala Trp
 1 5 10 15

gtc gcc gta tcc gag ctc aca cgc aac cac acc aaa cgc gcc tcc gca 96
 Val Ala Val Ser Glu Leu Thr Arg Asn His Thr Lys Arg Ala Ser Ala
 20 25 30

acc gtg aag acc gcc gta ttg gcg aca ctg ttg ttt gca acg gtt cag 144
 Thr Val Lys Thr Ala Val Leu Ala Thr Leu Leu Phe Ala Thr Val Gln
 35 40 45

gcg aat gct acc gat gaa gat gaa gaa gaa gag tta gaa tcc gta caa 192
 Ala Asn Ala Thr Asp Glu Asp Glu Glu Glu Glu Leu Glu Ser Val Gln
 50 55 60

cgc tct gtc gta ggg agc att caa gcc agt atg gaa ggc agc gtc gaa 240
 Arg Ser Val Val Gly Ser Ile Gln Ala Ser Met Glu Gly Ser Val Glu
 65 70 75 80

ttg gaa acg ata tca tta tca atg act aac gac agc aag gaa ttt gta 288
 Leu Glu Thr Ile Ser Leu Ser Met Thr Asn Asp Ser Lys Glu Phe Val
 85 90 95

gac cca tac ata gta gtt acc ctc aaa gcc ggc gac aac ctg aaa atc 336
 Asp Pro Tyr Ile Val Val Thr Leu Lys Ala Gly Asp Asn Leu Lys Ile
 100 105 110

aaa caa aac acc aat gaa aac acc aat gcc agt agc ttc acc tac tcg 384
 Lys Gln Asn Thr Asn Glu Asn Thr Asn Ala Ser Ser Phe Thr Tyr Ser
 115 120 125

ctg aaa aaa gac ctc aca ggc ctg atc aat gtt gaa act gaa aaa tta 432
 Leu Lys Lys Asp Leu Thr Gly Leu Ile Asn Val Glu Thr Glu Lys Leu
 130 135 140

tcg ttt ggc gca aac ggc aag aaa gtc aac atc ata agc gac acc aaa 480
 Ser Phe Gly Ala Asn Gly Lys Lys Val Asn Ile Ile Ser Asp Thr Lys
 145 150 155 160

ggc ttg aat ttc gcg aaa gaa acg gct ggg acg aac ggc gac acc acg 528
 Gly Leu Asn Phe Ala Lys Glu Thr Ala Gly Thr Asn Gly Asp Thr Thr
 165 170 175

gtt cat ctg aac ggt atc ggt tcg act ttg acc gat atg ctg ctg aat 576
 Val His Leu Asn Gly Ile Gly Ser Thr Leu Thr Asp Met Leu Leu Asn
 180 185 190

acc gga gcg acc aca aac gta acc aac gac aac gtt acc gat gac gag 624
 Thr Gly Ala Thr Thr Asn Val Thr Asn Asp Asn Val Thr Asp Asp Glu
 195 200 205

xxxiv

aaa	aaa	cgt	gcg	gca	agc	gtt	aaa	gac	gta	tta	aac	gca	ggc	tggt	aac	672
Lys	Lys	Arg	Ala	Ala	Ser	Val	Lys	Asp	Val	Leu	Asn	Ala	Gly	Trp	Asn	
	210					215					220					
att	aaa	ggc	gtt	aaa	ccc	ggg	aca	aca	gct	tcc	gat	aac	gtt	gat	ttc	720
Ile	Lys	Gly	Val	Lys	Pro	Gly	Thr	Thr	Ala	Ser	Asp	Asn	Val	Asp	Phe	
225					230					235					240	
gtc	cgc	act	tac	gac	aca	gtc	gag	ttc	ttg	agc	gca	gat	acg	aaa	aca	768
Val	Arg	Thr	Tyr	Asp	Thr	Val	Glu	Phe	Leu	Ser	Ala	Asp	Thr	Lys	Thr	
				245					250					255		
acg	act	gtt	aat	gtg	gaa	agc	aaa	gac	aac	ggc	aag	aaa	acc	gaa	gtt	816
Thr	Thr	Val	Asn	Val	Glu	Ser	Lys	Asp	Asn	Gly	Lys	Lys	Thr	Glu	Val	
			260					265					270			
aaa	atc	ggg	gcg	aag	act	tct	gtt	att	aaa	gaa	aaa	gac	ggg	aag	ttg	864
Lys	Ile	Gly	Ala	Lys	Thr	Ser	Val	Ile	Lys	Glu	Lys	Asp	Gly	Lys	Leu	
		275					280					285				
gtt	act	ggg	aaa	ggc	aaa	ggc	gag	aat	ggg	tct	tct	aca	gac	gaa	ggc	912
Val	Thr	Gly	Lys	Gly	Lys	Gly	Glu	Asn	Gly	Ser	Ser	Thr	Asp	Glu	Gly	
		290				295					300					
gaa	ggc	tta	gtg	act	gca	aaa	gaa	gtg	att	gat	gca	gta	aac	aag	gct	960
Glu	Gly	Leu	Val	Thr	Ala	Lys	Glu	Val	Ile	Asp	Ala	Val	Asn	Lys	Ala	
305					310					315					320	
ggg	tggt	aga	atg	aaa	aca	aca	acc	gct	aat	ggg	caa	aca	ggg	caa	gct	1008
Gly	Trp	Arg	Met	Lys	Thr	Thr	Thr	Ala	Asn	Gly	Gln	Thr	Gly	Gln	Ala	
				325					330					335		
gac	aag	ttt	gaa	acc	gtt	aca	tca	ggc	aca	aaa	gta	acc	ttt	gct	agt	1056
Asp	Lys	Phe	Glu	Thr	Val	Thr	Ser	Gly	Thr	Lys	Val	Thr	Phe	Ala	Ser	
			340					345					350			
ggg	aat	ggg	aca	act	gcg	act	gta	agt	aaa	gat	gat	caa	ggc	aac	atc	1104
Gly	Asn	Gly	Thr	Thr	Ala	Thr	Val	Ser	Lys	Asp	Asp	Gln	Gly	Asn	Ile	
		355					360					365				
act	gtt	aag	tat	gat	gta	aat	gtc	ggc	gat	gcc	cta	aac	gtc	aat	cag	1152
Thr	Val	Lys	Tyr	Asp	Val	Asn	Val	Gly	Asp	Ala	Leu	Asn	Val	Asn	Gln	
		370				375					380					
ctg	caa	aac	agc	ggg	tggt	aat	ttg	gat	tcc	aaa	ggc	gtt	gca	ggg	tct	1200
Leu	Gln	Asn	Ser	Gly	Trp	Asn	Leu	Asp	Ser	Lys	Ala	Val	Ala	Gly	Ser	
385					390					395					400	
tcg	ggc	aaa	gtc	atc	agc	ggc	aat	gtt	tcg	ccg	agc	aag	gga	aag	atg	1248
Ser	Gly	Lys	Val	Ile	Ser	Gly	Asn	Val	Ser	Pro	Ser	Lys	Gly	Lys	Met	
			405						410					415		
gat	gaa	acc	gtc	aac	att	aat	gcc	ggc	aac	aac	atc	gag	att	acc	cgc	1296
Asp	Glu	Thr	Val	Asn	Ile	Asn	Ala	Gly	Asn	Asn	Ile	Glu	Ile	Thr	Arg	
			420					425					430			
aac	ggc	aaa	aat	atc	gac	atc	gcc	act	tcg	atg	acc	ccg	caa	ttt	tcc	1344
Asn	Gly	Lys	Asn	Ile	Asp	Ile	Ala	Thr	Ser	Met	Thr	Pro	Gln	Phe	Ser	
		435					440					445				
agc	gtt	tcg	ctc	ggc	gcg	ggg	gcg	gat	gcg	ccc	act	tta	agc	gtg	gat	1392
Ser	Val	Ser	Leu	Gly	Ala	Gly	Ala	Asp	Ala	Pro	Thr	Leu	Ser	Val	Asp	
		450				455				460						
gac	gag	ggc	gcg	ttg	aat	gtc	ggc	agc	aag	gat	gcc	aac	aaa	ccc	gtc	1440

XXXV

Asp Glu Gly Ala Leu Asn Val Gly Ser Lys Asp Ala Asn Lys Pro Val
 465 470 475 480
 cgc att acc aat gtc gcc ccg ggc gtt aaa gag ggg gat gtt aca aac 1488
 Arg Ile Thr Asn Val Ala Pro Gly Val Lys Glu Gly Asp Val Thr Asn
 485 490 495
 gtc gcg caa ctt aaa ggt gtg gcg caa aac ttg aac aac cgc atc gac 1536
 Val Ala Gln Leu Lys Gly Val Ala Gln Asn Leu Asn Asn Arg Ile Asp
 500 505 510
 aat gtg aac ggc aac gcg cgt gcg ggc atc gcc caa gcg att gca acc 1584
 Asn Val Asn Gly Asn Ala Arg Ala Gly Ile Ala Gln Ala Ile Ala Thr
 515 520 525
 gca ggt ctg gtt cag gcg tat ctg ccc ggc aag agt atg atg gcg atc 1632
 Ala Gly Leu Val Gln Ala Tyr Leu Pro Gly Lys Ser Met Met Ala Ile
 530 535 540
 ggc ggc ggc act tat ctc ggc gaa gcc ggt tat gcc atc ggc tac tca 1680
 Gly Gly Gly Thr Tyr Leu Gly Glu Ala Gly Tyr Ala Ile Gly Tyr Ser
 545 550 555 560
 agc att tcc gcc ggc gga aat tgg att atc aaa ggc acg gct tcc ggc 1728
 Ser Ile Ser Ala Gly Gly Asn Trp Ile Ile Lys Gly Thr Ala Ser Gly
 565 570 575
 aat tcg cgc ggc cat ttc ggt gct tcc gca tct gtc ggt tat cag tgg 1776
 Asn Ser Arg Gly His Phe Gly Ala Ser Ala Ser Val Gly Tyr Gln Trp
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 taa 1779

<210> 17
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 <213> Neisseria meningitidis

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 35 40 45
 Ala Asn Ala Thr Asp Glu Asp Glu Glu Glu Glu Leu Glu Ser Val Gln
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 Arg Ser Val Val Gly Ser Ile Gln Ala Ser Met Glu Gly Ser Val Glu
 65 70 75 80
 Leu Glu Thr Ile Ser Leu Ser Met Thr Asn Asp Ser Lys Glu Phe Val
 85 90 95
 Asp Pro Tyr Ile Val Val Thr Leu Lys Ala Gly Asp Asn Leu Lys Ile
 100 105 110
 Lys Gln Asn Thr Asn Glu Asn Thr Asn Ala Ser Ser Phe Thr Tyr Ser
 115 120 125

XXXvi

Leu Lys Lys Asp Leu Thr Gly Leu Ile Asn Val Glu Thr Glu Lys Leu
 130 135 140
 Ser Phe Gly Ala Asn Gly Lys Lys Val Asn Ile Ile Ser Asp Thr Lys
 145 150 155 160
 Gly Leu Asn Phe Ala Lys Glu Thr Ala Gly Thr Asn Gly Asp Thr Thr
 165 170 175
 Val His Leu Asn Gly Ile Gly Ser Thr Leu Thr Asp Met Leu Leu Asn
 180 185 190
 Thr Gly Ala Thr Thr Asn Val Thr Asn Asp Asn Val Thr Asp Asp Glu
 195 200 205
 Lys Lys Arg Ala Ala Ser Val Lys Asp Val Leu Asn Ala Gly Trp Asn
 210 215 220
 Ile Lys Gly Val Lys Pro Gly Thr Thr Ala Ser Asp Asn Val Asp Phe
 225 230 235 240
 Val Arg Thr Tyr Asp Thr Val Glu Phe Leu Ser Ala Asp Thr Lys Thr
 245 250 255
 Thr Thr Val Asn Val Glu Ser Lys Asp Asn Gly Lys Lys Thr Glu Val
 260 265 270
 Lys Ile Gly Ala Lys Thr Ser Val Ile Lys Glu Lys Asp Gly Lys Leu
 275 280 285
 Val Thr Gly Lys Gly Lys Gly Glu Asn Gly Ser Ser Thr Asp Glu Gly
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 Glu Gly Leu Val Thr Ala Lys Glu Val Ile Asp Ala Val Asn Lys Ala
 305 310 315 320
 Gly Trp Arg Met Lys Thr Thr Thr Ala Asn Gly Gln Thr Gly Gln Ala
 325 330 335
 Asp Lys Phe Glu Thr Val Thr Ser Gly Thr Lys Val Thr Phe Ala Ser
 340 345 350
 Gly Asn Gly Thr Thr Ala Thr Val Ser Lys Asp Asp Gln Gly Asn Ile
 355 360 365
 Thr Val Lys Tyr Asp Val Asn Val Gly Asp Ala Leu Asn Val Asn Gln
 370 375 380
 Leu Gln Asn Ser Gly Trp Asn Leu Asp Ser Lys Ala Val Ala Gly Ser
 385 390 395 400
 Ser Gly Lys Val Ile Ser Gly Asn Val Ser Pro Ser Lys Gly Lys Met
 405 410 415
 Asp Glu Thr Val Asn Ile Asn Ala Gly Asn Asn Ile Glu Ile Thr Arg
 420 425 430
 Asn Gly Lys Asn Ile Asp Ile Ala Thr Ser Met Thr Pro Gln Phe Ser
 435 440 445
 Ser Val Ser Leu Gly Ala Gly Ala Asp Ala Pro Thr Leu Ser Val Asp
 450 455 460
 Asp Glu Gly Ala Leu Asn Val Gly Ser Lys Asp Ala Asn Lys Pro Val
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xxxviii

gag ctg aaa gac ctg acc agt gtt gaa act gaa aaa tta tcg ttt ggc	432
Glu Leu Lys Asp Leu Thr Ser Val Glu Thr Glu Lys Leu Ser Phe Gly	
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gca aac ggt aat aaa gtc aac atc aca agc gac acc aaa ggc ttg aat	480
Ala Asn Gly Asn Lys Val Asn Ile Thr Ser Asp Thr Lys Gly Leu Asn	
145 150 155 160	
ttt gcg aaa gaa acg gct ggg acg aac ggc gac ccc acg gtt cat ctg	528
Phe Ala Lys Glu Thr Ala Gly Thr Asn Gly Asp Pro Thr Val His Leu	
165 170 175	
aac ggt atc ggt tcg act ttg acc gat acg ctt gcg ggt tct tct gct	576
Asn Gly Ile Gly Ser Thr Leu Thr Asp Thr Leu Ala Gly Ser Ser Ala	
180 185 190	
tct cac gtt gat gcg ggt aac caa agt aca cat tac act cgt gca gca	624
Ser His Val Asp Ala Gly Asn Gln Ser Thr His Tyr Thr Arg Ala Ala	
195 200 205	
agt att aag gat gtg ttg aat gcg ggt tgg aat att aag ggt gtt aaa	672
Ser Ile Lys Asp Val Leu Asn Ala Gly Trp Asn Ile Lys Gly Val Lys	
210 215 220	
act ggc tca aca act ggt caa tca gaa aat gtc gat ttc gtc cgc act	720
Thr Gly Ser Thr Thr Gly Gln Ser Glu Asn Val Asp Phe Val Arg Thr	
225 230 235 240	
tac gac aca gtc gag ttc ttg agc gca gat acg aaa aca acg act gtt	768
Tyr Asp Thr Val Glu Phe Leu Ser Ala Asp Thr Lys Thr Thr Thr Val	
245 250 255	
aat gtg gaa agc aaa gac aac ggc aag aga acc gaa gtt aaa atc ggt	816
Asn Val Glu Ser Lys Asp Asn Gly Lys Arg Thr Glu Val Lys Ile Gly	
260 265 270	
gcg aag act tct gtt att aaa gaa aaa gac ggt aag ttg gtt act ggt	864
Ala Lys Thr Ser Val Ile Lys Glu Lys Asp Gly Lys Leu Val Thr Gly	
275 280 285	
aaa ggc aaa ggc gag aat ggt tct tct aca gac gaa ggc gaa ggc tta	912
Lys Gly Lys Gly Glu Asn Gly Ser Ser Thr Asp Glu Gly Glu Gly Leu	
290 295 300	
gtg act gca aaa gaa gtg att gat gca gta aac aag gct ggt tgg aga	960
Val Thr Ala Lys Glu Val Ile Asp Ala Val Asn Lys Ala Gly Trp Arg	
305 310 315 320	
atg aaa aca aca acc gct aat ggt caa aca ggt caa gct gac aag ttt	1008
Met Lys Thr Thr Thr Ala Asn Gly Gln Thr Gly Gln Ala Asp Lys Phe	
325 330 335	
gaa acc gtt aca tca ggc aca aaa gta acc ttt gct agt ggt aat ggt	1056
Glu Thr Val Thr Ser Gly Thr Lys Val Thr Phe Ala Ser Gly Asn Gly	
340 345 350	
aca act gcg act gta agt aaa gat gat caa ggc aac atc act gtt aag	1104
Thr Thr Ala Thr Val Ser Lys Asp Asp Gln Gly Asn Ile Thr Val Lys	
355 360 365	
tat gat gta aat gtc ggc gat gcc cta aac gtc aat cag ctg caa aac	1152
Tyr Asp Val Asn Val Gly Asp Ala Leu Asn Val Asn Gln Leu Gln Asn	
370 375 380	
agc ggt tgg aat ttg gat tcc aaa gcg gtt gca ggt tct tcg ggc aaa	1200

xxxix

Ser Gly Trp Asn Leu Asp Ser Lys Ala Val Ala Gly Ser Ser Gly Lys
 385 390 395 400

gtc atc agc ggc aat gtt tcg ccg agc aag gga aag atg gat gaa acc 1248
 Val Ile Ser Gly Asn Val Ser Pro Ser Lys Gly Lys Met Asp Glu Thr
 405 410 415

gtc aac att aat gcc ggc aac aac atc gag att acc cgc aac ggc aaa 1296
 Val Asn Ile Asn Ala Gly Asn Asn Ile Glu Ile Thr Arg Asn Gly Lys
 420 425 430

aat atc gac atc gcc act tcg atg acc ccg caa ttt tcc agc gtt tcg 1344
 Asn Ile Asp Ile Ala Thr Ser Met Thr Pro Gln Phe Ser Ser Val Ser
 435 440 445

ctc ggc gcg ggg gcg gat gcg ccc act tta agc gtg gat gac gag ggc 1392
 Leu Gly Ala Gly Ala Asp Ala Pro Thr Leu Ser Val Asp Asp Glu Gly
 450 455 460

gcg ttg aat gtc ggc agc aag gat gcc aac aaa ccc gtc cgc att acc 1440
 Ala Leu Asn Val Gly Ser Lys Asp Ala Asn Lys Pro Val Arg Ile Thr
 465 470 475

aat gtc gcc ccg ggc gtt aaa gag ggg gat gtt aca aac gtc gca caa 1488
 Asn Val Ala Pro Gly Val Lys Glu Gly Asp Val Thr Asn Val Ala Gln
 485 490 495

ctt aaa ggt gtg gcg caa aac ttg aac aac cgc atc gac aat gtg aac 1536
 Leu Lys Gly Val Ala Gln Asn Leu Asn Asn Arg Ile Asp Asn Val Asn
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ggc aac gcg cgc gcg ggt atc gcc caa gcg att gca acc gca ggt ttg 1584
 Gly Asn Ala Arg Ala Gly Ile Ala Gln Ala Ile Ala Thr Ala Gly Leu
 515 520 525

gct cag gcc tat ttg ccc ggc aag agt atg atg gcg atc ggc ggc ggt 1632
 Ala Gln Ala Tyr Leu Pro Gly Lys Ser Met Met Ala Ile Gly Gly Gly
 530 535 540

act tat ctc ggc gaa gcc ggt tac gcc atc ggc tac tcg agc att tct 1680
 Thr Tyr Leu Gly Glu Ala Gly Tyr Ala Ile Gly Tyr Ser Ser Ile Ser
 545 550 555 560

gac act ggg aat tgg gtt atc aag ggc acg gct tcc ggc aat tcg cgc 1728
 Asp Thr Gly Asn Trp Val Ile Lys Gly Thr Ala Ser Gly Asn Ser Arg
 565 570 575

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 580 585 590

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 <213> Neisseria meningitidis

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 20 25 30

Thr Val Ala Thr Ala Val Leu Ala Thr Leu Leu Ser Ala Thr Val Gln

xl

35					40					45					
Ala	Asn	Ala	Thr	Asp	Thr	Asp	Glu	Asp	Glu	Glu	Leu	Glu	Ser	Val	Ala
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Arg	Ser	Ala	Leu	Val	Leu	Gln	Phe	Met	Ile	Asp	Lys	Glu	Gly	Asn	Gly
65					70					75					80
Glu	Ile	Glu	Ser	Thr	Gly	Asp	Ile	Gly	Trp	Ser	Ile	Tyr	Tyr	Asp	Asp
				85					90					95	
His	Asn	Thr	Leu	His	Gly	Ala	Thr	Val	Thr	Leu	Lys	Ala	Gly	Asp	Asn
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Leu	Lys	Ile	Lys	Gln	Ser	Gly	Lys	Asp	Phe	Thr	Tyr	Ser	Leu	Lys	Lys
		115					120					125			
Glu	Leu	Lys	Asp	Leu	Thr	Ser	Val	Glu	Thr	Glu	Lys	Leu	Ser	Phe	Gly
	130						135				140				
Ala	Asn	Gly	Asn	Lys	Val	Asn	Ile	Thr	Ser	Asp	Thr	Lys	Gly	Leu	Asn
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Phe	Ala	Lys	Glu	Thr	Ala	Gly	Thr	Asn	Gly	Asp	Pro	Thr	Val	His	Leu
				165					170					175	
Asn	Gly	Ile	Gly	Ser	Thr	Leu	Thr	Asp	Thr	Leu	Ala	Gly	Ser	Ser	Ala
			180					185					190		
Ser	His	Val	Asp	Ala	Gly	Asn	Gln	Ser	Thr	His	Tyr	Thr	Arg	Ala	Ala
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Ser	Ile	Lys	Asp	Val	Leu	Asn	Ala	Gly	Trp	Asn	Ile	Lys	Gly	Val	Lys
	210					215					220				
Thr	Gly	Ser	Thr	Thr	Gly	Gln	Ser	Glu	Asn	Val	Asp	Phe	Val	Arg	Thr
225					230					235					240
Tyr	Asp	Thr	Val	Glu	Phe	Leu	Ser	Ala	Asp	Thr	Lys	Thr	Thr	Thr	Val
				245					250					255	
Asn	Val	Glu	Ser	Lys	Asp	Asn	Gly	Lys	Arg	Thr	Glu	Val	Lys	Ile	Gly
			260					265					270		
Ala	Lys	Thr	Ser	Val	Ile	Lys	Glu	Lys	Asp	Gly	Lys	Leu	Val	Thr	Gly
		275					280					285			
Lys	Gly	Lys	Gly	Glu	Asn	Gly	Ser	Ser	Thr	Asp	Glu	Gly	Glu	Gly	Leu
	290					295					300				
Val	Thr	Ala	Lys	Glu	Val	Ile	Asp	Ala	Val	Asn	Lys	Ala	Gly	Trp	Arg
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Met	Lys	Thr	Thr	Thr	Ala	Asn	Gly	Gln	Thr	Gly	Gln	Ala	Asp	Lys	Phe
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Glu	Thr	Val	Thr	Ser	Gly	Thr	Lys	Val	Thr	Phe	Ala	Ser	Gly	Asn	Gly
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Thr	Thr	Ala	Thr	Val	Ser	Lys	Asp	Asp	Gln	Gly	Asn	Ile	Thr	Val	Lys
		355					360					365			
Tyr	Asp	Val	Asn	Val	Gly	Asp	Ala	Leu	Asn	Val	Asn	Gln	Leu	Gln	Asn
	370					375					380				

xli

Ser Gly Trp Asn Leu Asp Ser Lys Ala Val Ala Gly Ser Ser Gly Lys
 385 390 395 400
 Val Ile Ser Gly Asn Val Ser Pro Ser Lys Gly Lys Met Asp Glu Thr
 405 410 415
 Val Asn Ile Asn Ala Gly Asn Asn Ile Glu Ile Thr Arg Asn Gly Lys
 420 425 430
 Asn Ile Asp Ile Ala Thr Ser Met Thr Pro Gln Phe Ser Ser Val Ser
 435 440 445
 Leu Gly Ala Gly Ala Asp Ala Pro Thr Leu Ser Val Asp Asp Glu Gly
 450 455 460
 Ala Leu Asn Val Gly Ser Lys Asp Ala Asn Lys Pro Val Arg Ile Thr
 465 470 475 480
 Asn Val Ala Pro Gly Val Lys Glu Gly Asp Val Thr Asn Val Ala Gln
 485 490 495
 Leu Lys Gly Val Ala Gln Asn Leu Asn Asn Arg Ile Asp Asn Val Asn
 500 505 510
 Gly Asn Ala Arg Ala Gly Ile Ala Gln Ala Ile Ala Thr Ala Gly Leu
 515 520 525
 Ala Gln Ala Tyr Leu Pro Gly Lys Ser Met Met Ala Ile Gly Gly Gly
 530 535 540
 Thr Tyr Leu Gly Glu Ala Gly Tyr Ala Ile Gly Tyr Ser Ser Ile Ser
 545 550 555 560
 Asp Thr Gly Asn Trp Val Ile Lys Gly Thr Ala Ser Gly Asn Ser Arg
 565 570 575
 Gly His Phe Gly Thr Ser Ala Ser Val Gly Tyr Gln Trp
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 gtc gtc gta tcc gag ctc aca cgc aac cac acc aaa cgc gcc tcc gca 96
 Val Val Val Ser Glu Leu Thr Arg Asn His Thr Lys Arg Ala Ser Ala
 20 25 30
 acc gtg aag acc gcc gta ttg gcg act ctg ttg ttt gca acg gtt cag 144
 Thr Val Lys Thr Ala Val Leu Ala Thr Leu Leu Phe Ala Thr Val Gln
 35 40 45
 gca agt gct aac aat gaa gag caa gaa gaa gat tta tat tta gac ccc 192
 Ala Ser Ala Asn Asn Glu Glu Gln Glu Glu Asp Leu Tyr Leu Asp Pro
 50 55 60

xlii

gta	caa	cgc	act	gtt	gcc	gtg	ttg	ata	gtc	aat	tcc	gat	aaa	gaa	ggc	240
Val	Gln	Arg	Thr	Val	Ala	Val	Leu	Ile	Val	Asn	Ser	Asp	Lys	Glu	Gly	
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acg	gga	gaa	aaa	gaa	aaa	gta	gaa	gaa	aat	tca	gat	tgg	gca	gta	tat	288
Thr	Gly	Glu	Lys	Glu	Lys	Val	Glu	Glu	Asn	Ser	Asp	Trp	Ala	Val	Tyr	
				85					90					95		
ttc	aac	gag	aaa	gga	gta	cta	aca	gcc	aga	gaa	atc	acc	ctc	aaa	gcc	336
Phe	Asn	Glu	Lys	Gly	Val	Leu	Thr	Ala	Arg	Glu	Ile	Thr	Leu	Lys	Ala	
			100					105					110			
ggc	gac	aac	ctg	aaa	atc	aaa	caa	aac	ggc	aca	aac	ttc	acc	tac	tcg	384
Gly	Asp	Asn	Leu	Lys	Ile	Lys	Gln	Asn	Gly	Thr	Asn	Phe	Thr	Tyr	Ser	
		115					120					125				
ctg	aaa	aaa	gac	ctc	aca	gat	ctg	acc	agt	gtt	gga	act	gaa	aaa	tta	432
Leu	Lys	Lys	Asp	Leu	Thr	Asp	Leu	Thr	Ser	Val	Gly	Thr	Glu	Lys	Leu	
	130					135					140					
tcg	ttt	agc	gca	aac	ggc	aat	aaa	gtc	aac	atc	aca	agc	gac	acc	aaa	480
Ser	Phe	Ser	Ala	Asn	Gly	Asn	Lys	Val	Asn	Ile	Thr	Ser	Asp	Thr	Lys	
145					150					155					160	
ggc	ttg	aat	ttt	gcg	aaa	gaa	acg	gct	ggg	acg	aac	ggc	gac	acc	acg	528
Gly	Leu	Asn	Phe	Ala	Lys	Glu	Thr	Ala	Gly	Thr	Asn	Gly	Asp	Thr	Thr	
				165					170					175		
gtt	cat	ctg	aac	ggt	att	ggt	tcg	act	ttg	acc	gat	acg	ctg	ctg	aat	576
Val	His	Leu	Asn	Gly	Ile	Gly	Ser	Thr	Leu	Thr	Asp	Thr	Leu	Leu	Asn	
			180					185					190			
acc	gga	gcg	acc	aca	aac	gta	acc	aac	gac	aac	gtt	acc	gat	gac	gag	624
Thr	Gly	Ala	Thr	Thr	Asn	Val	Thr	Asn	Asp	Asn	Val	Thr	Asp	Asp	Glu	
		195					200					205				
aaa	aaa	cgt	gcg	gca	agc	gtt	aaa	gac	gta	tta	aac	gct	ggc	tgg	aac	672
Lys	Lys	Arg	Ala	Ala	Ser	Val	Lys	Asp	Val	Leu	Asn	Ala	Gly	Trp	Asn	
	210					215					220					
att	aaa	ggc	gtt	aaa	ccc	ggt	aca	aca	gct	tcc	gat	aac	gtt	gat	ttc	720
Ile	Lys	Gly	Val	Lys	Pro	Gly	Thr	Thr	Ala	Ser	Asp	Asn	Val	Asp	Phe	
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gtc	cgc	act	tac	gac	aca	gtc	gag	ttc	ttg	agc	gca	gat	acg	aaa	aca	768
Val	Arg	Thr	Tyr	Asp	Thr	Val	Glu	Phe	Leu	Ser	Ala	Asp	Thr	Lys	Thr	
				245					250					255		
acg	act	gtt	aat	gtg	gaa	agc	aaa	gac	aac	ggc	aag	aaa	acc	gaa	gtt	816
Thr	Thr	Val	Asn	Val	Glu	Ser	Lys	Asp	Asn	Gly	Lys	Lys	Thr	Glu	Val	
			260					265					270			
aaa	atc	ggt	gcg	aag	act	tct	gtt	att	aaa	gaa	aaa	gac	ggt	aag	ttg	864
Lys	Ile	Gly	Ala	Lys	Thr	Ser	Val	Ile	Lys	Glu	Lys	Asp	Gly	Lys	Leu	
		275					280					285				
gtt	act	ggt	aaa	gac	aaa	ggc	gag	aat	ggt	tct	tct	aca	gac	gaa	ggc	912
Val	Thr	Gly	Lys	Asp	Lys	Gly	Glu	Asn	Gly	Ser	Ser	Thr	Asp	Glu	Gly	
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gaa	ggc	tta	gtg	act	gca	aaa	gaa	gtg	att	gat	gca	gta	aac	aag	gct	960
Glu	Gly	Leu	Val	Thr	Ala	Lys	Glu	Val	Ile	Asp	Ala	Val	Asn	Lys	Ala	
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xliiii

ggt tgg aga atg aaa aca aca acc gct aat ggt caa aca ggt caa gct	1008
Gly Trp Arg Met Lys Thr Thr Thr Ala Asn Gly Gln Thr Gly Gln Ala	
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gac aag ttt gaa acc gtt aca tca ggc aca aat gta acc ttt gct agt	1056
Asp Lys Phe Glu Thr Val Thr Ser Gly Thr Asn Val Thr Phe Ala Ser	
340 345 350	
ggt aaa ggt aca act gcg act gta agt aaa gat gat caa ggc aac atc	1104
Gly Lys Gly Thr Thr Ala Thr Val Ser Lys Asp Asp Gln Gly Asn Ile	
355 360 365	
act gtt atg tat gat gta aat gtc ggc gat gcc cta aac gtc aat cag	1152
Thr Val Met Tyr Asp Val Asn Val Gly Asp Ala Leu Asn Val Asn Gln	
370 375 380	
ctg caa aac agc ggt tgg aat ttg gat tcc aaa gcg gtt gca ggt tct	1200
Leu Gln Asn Ser Gly Trp Asn Leu Asp Ser Lys Ala Val Ala Gly Ser	
385 390 395 400	
tcg ggc aaa gtc atc agc ggc aat gtt tcg ccg agc aag gga aag atg	1248
Ser Gly Lys Val Ile Ser Gly Asn Val Ser Pro Ser Lys Gly Lys Met	
405 410 415	
gat gaa acc gtc aac att aat gcc ggc aac aac atc gag att acc cgc	1296
Asp Glu Thr Val Asn Ile Asn Ala Gly Asn Asn Ile Glu Ile Thr Arg	
420 425 430	
aac ggt aaa aat atc gac atc gcc act tcg atg acc ccg cag ttt tcc	1344
Asn Gly Lys Asn Ile Asp Ile Ala Thr Ser Met Thr Pro Gln Phe Ser	
435 440 445	
agc gtt tcg ctc ggc gcg ggg gcg gat gcg ccc act ttg agc gtg gat	1392
Ser Val Ser Leu Gly Ala Gly Ala Asp Ala Pro Thr Leu Ser Val Asp	
450 455 460	
ggg gac gca ttg aat gtc ggc agc aag aag gac aac aaa ccc gtc cgc	1440
Gly Asp Ala Leu Asn Val Gly Ser Lys Lys Asp Asn Lys Pro Val Arg	
465 470 475 480	
att acc aat gtc gcc ccg ggc gtt aaa gag ggg gat gtt aca aac gtc	1488
Ile Thr Asn Val Ala Pro Gly Val Lys Glu Gly Asp Val Thr Asn Val	
485 490 495	
gca caa ctt aaa ggc gtg gcg caa aac ttg aac aac cgc atc gac aat	1536
Ala Gln Leu Lys Gly Val Ala Gln Asn Leu Asn Asn Arg Ile Asp Asn	
500 505 510	
gtg gac ggc aac gcg cgt gcg ggc atc gcc caa gcg att gca acc gca	1584
Val Asp Gly Asn Ala Arg Ala Gly Ile Ala Gln Ala Ile Ala Thr Ala	
515 520 525	
ggt ctg gtt cag gcg tat ttg ccc ggc aag agt atg atg gcg atc ggc	1632
Gly Leu Val Gln Ala Tyr Leu Pro Gly Lys Ser Met Met Ala Ile Gly	
530 535 540	
ggc ggc act tat cgc ggc gaa gcc ggt tac gcc atc ggc tac tcc agt	1680
Gly Gly Thr Tyr Arg Gly Glu Ala Gly Tyr Ala Ile Gly Tyr Ser Ser	
545 550 555 560	
att tcc gac ggc gga aat tgg att atc aaa ggc acg gct tcc ggc aat	1728
Ile Ser Asp Gly Gly Asn Trp Ile Ile Lys Gly Thr Ala Ser Gly Asn	
565 570 575	
tcg cgc ggc cat ttc ggt gct tcc gca tct gtc ggt tat cag tgg taa	1776

xliv

Ser Arg Gly His Phe Gly Ala Ser Ala Ser Val Gly Tyr Gln Trp
 580 585 590

<210> 21
 <211> 591
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<400> 21
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 Thr Val Lys Thr Ala Val Leu Ala Thr Leu Leu Phe Ala Thr Val Gln
 35 40 45
 Ala Ser Ala Asn Asn Glu Glu Gln Glu Asp Leu Tyr Leu Asp Pro
 50 55 60
 Val Gln Arg Thr Val Ala Val Leu Ile Val Asn Ser Asp Lys Glu Gly
 65 70 75 80
 Thr Gly Glu Lys Glu Lys Val Glu Glu Asn Ser Asp Trp Ala Val Tyr
 85 90 95
 Phe Asn Glu Lys Gly Val Leu Thr Ala Arg Glu Ile Thr Leu Lys Ala
 100 105 110
 Gly Asp Asn Leu Lys Ile Lys Gln Asn Gly Thr Asn Phe Thr Tyr Ser
 115 120 125
 Leu Lys Lys Asp Leu Thr Asp Leu Thr Ser Val Gly Thr Glu Lys Leu
 130 135 140
 Ser Phe Ser Ala Asn Gly Asn Lys Val Asn Ile Thr Ser Asp Thr Lys
 145 150 155 160
 Gly Leu Asn Phe Ala Lys Glu Thr Ala Gly Thr Asn Gly Asp Thr Thr
 165 170 175
 Val His Leu Asn Gly Ile Gly Ser Thr Leu Thr Asp Thr Leu Leu Asn
 180 185 190
 Thr Gly Ala Thr Thr Asn Val Thr Asn Asp Asn Val Thr Asp Asp Glu
 195 200 205
 Lys Lys Arg Ala Ala Ser Val Lys Asp Val Leu Asn Ala Gly Trp Asn
 210 215 220
 Ile Lys Gly Val Lys Pro Gly Thr Thr Ala Ser Asp Asn Val Asp Phe
 225 230 235 240
 Val Arg Thr Tyr Asp Thr Val Glu Phe Leu Ser Ala Asp Thr Lys Thr
 245 250 255
 Thr Thr Val Asn Val Glu Ser Lys Asp Asn Gly Lys Lys Thr Glu Val
 260 265 270
 Lys Ile Gly Ala Lys Thr Ser Val Ile Lys Glu Lys Asp Gly Lys Leu
 275 280 285
 Val Thr Gly Lys Asp Lys Gly Glu Asn Gly Ser Ser Thr Asp Glu Gly

xlv

290	295	300
Glu Gly Leu Val Thr Ala Lys Glu Val Ile Asp Ala Val Asn Lys Ala		
305	310	315 320
Gly Trp Arg Met Lys Thr Thr Thr Ala Asn Gly Gln Thr Gly Gln Ala		
	325	330 335
Asp Lys Phe Glu Thr Val Thr Ser Gly Thr Asn Val Thr Phe Ala Ser		
	340	345 350
Gly Lys Gly Thr Thr Ala Thr Val Ser Lys Asp Asp Gln Gly Asn Ile		
	355	360 365
Thr Val Met Tyr Asp Val Asn Val Gly Asp Ala Leu Asn Val Asn Gln		
	370	375 380
Leu Gln Asn Ser Gly Trp Asn Leu Asp Ser Lys Ala Val Ala Gly Ser		
	385	390 395 400
Ser Gly Lys Val Ile Ser Gly Asn Val Ser Pro Ser Lys Gly Lys Met		
	405	410 415
Asp Glu Thr Val Asn Ile Asn Ala Gly Asn Asn Ile Glu Ile Thr Arg		
	420	425 430
Asn Gly Lys Asn Ile Asp Ile Ala Thr Ser Met Thr Pro Gln Phe Ser		
	435	440 445
Ser Val Ser Leu Gly Ala Gly Ala Asp Ala Pro Thr Leu Ser Val Asp		
	450	455 460
Gly Asp Ala Leu Asn Val Gly Ser Lys Lys Asp Asn Lys Pro Val Arg		
	465	470 475 480
Ile Thr Asn Val Ala Pro Gly Val Lys Glu Gly Asp Val Thr Asn Val		
	485	490 495
Ala Gln Leu Lys Gly Val Ala Gln Asn Leu Asn Asn Arg Ile Asp Asn		
	500	505 510
Val Asp Gly Asn Ala Arg Ala Gly Ile Ala Gln Ala Ile Ala Thr Ala		
	515	520 525
Gly Leu Val Gln Ala Tyr Leu Pro Gly Lys Ser Met Met Ala Ile Gly		
	530	535 540
Gly Gly Thr Tyr Arg Gly Glu Ala Gly Tyr Ala Ile Gly Tyr Ser Ser		
	545	550 555 560
Ile Ser Asp Gly Gly Asn Trp Ile Ile Lys Gly Thr Ala Ser Gly Asn		
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Ser Arg Gly His Phe Gly Ala Ser Ala Ser Val Gly Tyr Gln Trp		
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<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: 5'
oligonucleotide primer for PCR

xlvi

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<210> 23
<211> 18
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<210> 24
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<210> 26
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xlvii

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oligonucleotide primer for PCR

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18

<210> 29
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oligonucleotide primer for PCR

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18

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oligonucleotide primer for PCR

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18

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU 98/01031

A. CLASSIFICATION OF SUBJECT MATTERInt Cl⁶: C07K 14/22; C12N 15/31

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int Cl⁶: C07K 14/22; C12N 15/31Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
As below

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA)		TREMBL)	
WPAT)	Neisseria meningitidis adhesins	GENPEPT)	Applicant's sequences
Medline)		SWISS PROT PIR)	

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	VIRGI, M. Adv. in Exp. Med and Biol. 1996. 408: 113-122	ALL
A	RUDEL, T. et al. Nature 1995. 373: 357-359	ALL
A	VIRGI, M. et al. Mol Microbiol. 1992. 6(19): 2785-2795	ALL

☐ Further documents are listed in the
continuation of Box C

☐ See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

7 January 1999

Date of mailing of the international search report

21 JAN 1999

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INTERNATIONAL SEARCH REPORT

international application No.
PCT/AU 98/01031

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: (A) 2, 3, 5, 6, 7, 9; (B) 20(1) and 21
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
(A) Claims 2, 3, 5, 6, 7, 9 are not clear. They are essentially to polypeptides which have immunological activity against themselves or their parent organism (*Neisseria meningitidis*). This concept is virtually meaningless.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

continued

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU 98/01031

Box BOX 1 (2)

Antigens do not display immunological activity against themselves, or the organism from which they derive. However, as far as I can determine, these claims are intended to encompass either:

- (i) antigenic polypeptides or their encoding nucleic acids according to claims 1, 4 or 7, which provide protective immunity to an animal or human against *Neisseria meningitidis* infection, or
- (ii) antibodies to such antigenic polypeptides.

Since these concepts are covered by other claims the lack of search on these claims does not affect the search coverage of the claims in toto.

- (B) Claims 20(1) and 21 are to any antibodies against *Neisseria meningitidis*. They lack support from the description as they are not limited to antibodies to the polypeptides of the invention.